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THE PROBLEM OF PRIMARY SCIATIC NEURITIS

(AN ANALYSIS OF 55 CASES.)

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THE need for an analysis of a group of cases of sciatic neuritis may occasion some surprise. When, however, one reads that "from the reports in the literature it seems evident that there are very few cases of primary sciatic pain,"[5] it becomes clear that it would be necessary to readjust one's ideas concerning sciatic neuritis if this statement were to be accepted at its face value. This concept, strange as it may appear to many, is supported further by the study of Grossman and Keschner,[11] who assert that "a primary mononeuritis or radiculitis of the sciatic nerve is extremely rare" and that practically all the cases of sciatica are secondary in origin. The tendency further to regard sciatic neuritis as a secondary manifestation of an osteoarthritis of the lumbar spine, with which it is assumed to be synonymous,[6] makes a study of cases of sciatic neuritis or primary sciatica still more pertinent. Add to this the recent popularity of nucleus pulposus herniations as a cause of sciatica, and it becomes clear that the entire group of sciatica cases requires urgent analysis, particularly with reference to accurate means of differentiating cases of sciatic neuritis or primary sciatica from those of secondary sciatica.

If it is true that, as some believe, primary sciatica or sciatic neuritis is rare, it becomes necessary to analyze the cases which are regarded by neurologists as examples of this disease. Here one immediately encounters a paradox, for what is regarded by the neurologist as sciatic neuritis is believed by the orthopedist to be secondary to a distant irritative factor. With a larger view of the

many secondary causes of sciatica, some of which have been only recently revealed, it seems more consistent with the facts to state, not that sciatic neuritis is rare, but that secondary sciatica is much more common as a cause of sciatic pain, and that as compared with secondary causes, primary sciatica or sciatic neuritis is less common in the production of sciatic pain. This is somewhat different from the tendency to read sciatic neuritis out of the sciatica party. Because of these inconsistencies, we have reviewed our cases of sciatic neuritis in order to establish primarily the incidence of sciatic neuritis and to determine its recognition from other cases of sciatica.

Analysis of Material. All 55 cases, available for study, were carefully selected as authentic examples of sciatic neuritis. Cases of secondary sciatica were discarded. It was our desire to study the symptomatology as well as to indicate differences between the symptoms and course of primary and secondary sciatica.

Sex. The majority of our cases were found in males. Of 55 cases, 37 (67%) were males and 18 females. This coincides with the experience of others, but gives a somewhat higher incidence in males than do other series of sciatic neuritis.

Occupation. The incidence of sciatic neuritis in the more strenuous sex is borne out also by an analysis of the occupations of our 55 cases. It has been pointed out by many others that sciatic neuritis and sciatica are more prone to occur in persons who are exposed to changes in weather, or who are engaged in strenuous occupations. All but 4 of the males in our series were engaged in heavy work. Listed among the occupations were laborers, miners, street cleaners, shoemakers, machinist, engineer, roofer, cab driver, seaman, auto mechanic and so forth. In by far the greater number of cases the occupation involved exposure to changes in weather, and the use of brawn. In 4 cases there was nothing in the occupation of significance. Opposed to this array of brawny occupations stands the occurrence of sciatic neuritis in the women of our series, most of them occurring in housewives. Three cases developed in nurses.

Age. The age incidence varies from 16 to 72 years. The majority (41) of our cases occurred between the ages of 30 and 60 (73%).

TABLE 1.—AGE INCIDENCE OF 55 CASES OF SCIATIC NEURITIS

Age	No. of cases
10–20	1
20–30	7
30–40	17
40–50	14
50–60	10
60–70	4
70–80	2

Sciatic neuritis therefore is a disease of middle and early old age, most of the cases occurring between 30 and 60 years of age, but it may develop before 30 and beyond 60 years.

Presenting Symptom. The presenting symptom in the majority of cases was pain referable to the hip or leg of one side. This pain often began in the hip and extended down the entire leg or only from the hip or back to the thigh. The presenting symptom was pain in the back.

Back Pain. Back pain is not a common symptom in sciatic neuritis. It was found in 17 of our 55 cases (about 30%). This is a low incidence if one were to take literally the assertion made by many authors that "sciatica" begins with an attack of lumbago which often persists late in the course of the illness. Its occurrence is of some value in differentiating between a primary sciatic neuritis and a secondary sciatica due to herniated nucleus pulposus, cauda equina tumor, structural deformity of the vertebræ, or one of the multifarious causes of the sciatic syndrome. While back pain occurs in one-third of the cases of sciatic neuritis it is more common in secondary sciatica.

Leg Pain. In 3 cases the pain was bilateral: all the others were unilateral. These cases however serve to emphasize the fact that bilateral sciatic pain may be due to a true neuritis, and need not necessarily indicate a tumor of the spinal cord. The old dictum that bilateral sciatic pain is always the result of structural causes needs revision, and this has come to be recognized by other investigators. Undoubtedly the majority of cases of bilateral sciatic pain are due to what may be termed structural causes such as tumor, arachnoiditis, or metastatic carcinoma, but the fact that pain in both legs may also be found in unqualified cases of sciatic neuritis needs to be more clearly recognized.

The *location* of the leg pain varies widely. It may be felt along the entire course of the sciatic nerve or in only portions of it.

TABLE 2.—DISTRIBUTION OF LEG PAIN IN 55 CASES OF SCIATIC NEURITIS

Location	No. of cases
Hip alone	0
Hip-thigh	10
Leg-ankle	15
Leg-toes or heel	14
Hip-knee	7
Thigh-calf	2
Knee-toes	2
Sacro-iliac	5

In the majority of the cases the pain extended from the thigh in the region of the hip to the ankle, toes or heel (29 cases). In some instances it extended from the hip to the thigh (10 cases), from the hip to the knee (7 cases), from the thigh to the calf (2 cases), or even from the knee to the toes (2 cases). In 5 cases the pain was in the sacro-iliac region without radiation.

The *duration* of the pain is of extreme interest. Sciatic neuritis is regarded as an acute disease, yet the incidence of prolonged pain is astoundingly high.

TABLE 3.—DURATION OF PAIN IN 55 CASES OF SCIATIC NEURITIS

Duration	No. of cases
1 week	1
3–4 weeks	10
5–8 "	13
9–12 "	5
3–6 months	9
7–10 "	2
10–12 "	2
1–2 years	6
3–5 "	7

Over half of the cases lasted from 1 to 12 weeks (29 cases), most of these lasting 3 to 8 weeks. Only 1 case lasted 1 week, the majority of the others persisting from 3 to 12 weeks. Nine cases lasted 3 to 6 months, and 13 cases from 1 to 5 years.

The cases lasting 3 to 12 weeks may be regarded as having a normal life history for sciatic neuritis, and as conforming to the generally accepted ideas concerning the duration of this illness. It is the instances of longer duration however which are of greatest interest, for it is when cases of sciatic neuritis stretch into periods of 6 months to 1 year or longer that doubt arises concerning the diagnosis. For this reason it is of paramount importance to know whether cases of sciatic neuritis may in fact last so long, and if so how they may be differentiated from cases of sciatic syndrome or secondary sciatica. A study of the cases which persisted for 1 year or more reveals the fact that in practically all these patients there were repeated attacks of sciatic neuritis. This group of cases represents therefore patients who have had recurrent attacks of sciatic neuritis lasting from 1 to 8 years. Of our 55 cases of sciatic neuritis, 13 (23%) may be regarded as recurrent. The duration of each episode of neuritis and the intervals during which the patient was free of pain could not be determined from the data at hand, the fact which seemed clearest being the tendency in these instances to recurrence of the attack of sciatic neuritis. The pattern of the attack as shown by the distribution of the pain and its nature varied often from one attack to another, but in some cases the distribution of the pain was the same with each repeated episode. These long cases of sciatic neuritis are of more than passing interest for they fall into a group in which, by virtue of duration of disease alone, the possibility of a secondary cause for the neuritis becomes pertinent. In most instances, when a case of sciatica which is assumed to be a sciatic neuritis lasts 2 to 5 years and is featured by recurrence of the sciatic pain, some secondary cause may be justifiably sought. The fact remains however that true sciatic neuritis may persist for long periods and that it need not be due to intraspinal or other causes. This is especially pertinent at the present time when, by virtue of advanced neurosurgical techniques, it is becoming a relatively common procedure to perform laminectomies on such cases. The point at issue is that mere longevity of symptoms is no indication of a

secondary cause of the sciatica unless other findings such as Roentgen-ray changes in the vertebræ and increased spinal fluid protein are present.

Little of clinical value is to be learned from the nature of the pain in the leg. It may be constant or intermittent. As a rule, for each particular attack it is constant, but it may be intermittent, with free intervals of pain for long periods or for very short periods. The pain is felt in the whole leg or in part of it and is not, as a rule, of a lancinating character. It is variously described as a dull ache or a sharp pain of various sorts, but little can be learned from the type of pain. Much more is to be learned from its distribution.

Movements of most sorts appear to increase the pain. It is almost invariably aggravated by walking, but frequently sitting, standing, or bending increases it. In some cases it is made worse by coughing, sneezing, or straining, all of which are frequently referred to as indicating evidence of a root lesion. In a few cases the pain is relieved by standing and aggravated by lying down. In general it seems clear that all movements which stretch the sciatic nerve, or which tend to stretch the muscles which are in spasm will produce an increase of the sciatic pain.

Paresthesias. Despite the fact that paresthesias are regarded as part of neuritis symptomatology, it is surprising to find how few of our cases complained of them. Only 7 of the 55 cases had paresthesias, variously referred to the back of the leg or thigh and sometimes in the foot.

Incontinence. In no case was there incontinence of the bladder or rectum, as was to be expected in cases of purely peripheral neuritis.

Nerve Tenderness. Nerve tenderness was found in 46 of 55 cases. The tenderness of the nerve was not always found along the entire length of the sciatic nerve. It was usually found everywhere along the sciatic trunk; in some cases only in the sciatic notch. Furthermore, muscle tenderness did not parallel nerve tenderness. The latter was almost always more pronounced than the tenderness of the muscles and was nowhere nearly as constant. It was a common experience to find nerve tenderness with little or no muscle tenderness. The stage of the sciatic neuritis must, of course, be considered in evaluating this feature, for it is quite possible that cases which had persisted for some time may have lost much of their muscle or nerve tenderness by the time they entered the hospital.

Lasègue's Sign. This, the sign of straight leg raising by which the sciatic nerve is stretched, was absent in only 7 or our cases. It is almost constant and is a sign of great importance, though it is by no means pathognomonic of sciatic neuritis. It is found as well in cases of sciatic syndrome due to many other causes.

In a few cases tenderness was found along the lumbar spinous processes, but the number of instances was not great enough to have any significance.

Reflex Changes. The Achilles reflex was decreased or absent on the side of the neuritis in 36 cases. In the other 19 cases it was

normal. The patellar reflex was never abnormal and no pathologic reflexes were found at any time.

Muscle weakness was found in none of our cases. It was surprising to find moreover that even in the long-standing recurrent cases no muscle atrophy was visible. In none of our cases was the muscle weakness ever of a greater degree than could be accounted for by protection against leg pain. This held true even in cases of long duration and it may be a point of value in differentiating cases of sciatic neuritis from those of secondary sciatica. While muscle weakness is by no means constant in the latter, its mere occurrence would tend to favor secondary sciatica, judged by its absence in our group of cases of sciatic neuritis.

Sensory Changes. These also were strikingly absent in almost all the cases except for a few with slightly decreased pain sensations over the lateral aspect of the thigh or leg. Sensory changes like muscle weakness and wasting were strikingly absent in the great majority of cases no matter what the duration of the disease.

Analysis of Causes. The analysis of causes of our cases of sciatic neuritis is, of course, difficult. Preëminent among the causes which stand out are those related to foci of infection. Diseased tonsils were found in 28 cases. This does not mean, of course, that tonsillar disease was responsible for the sciatic neuritis in all these instances. In only 8 cases could it be demonstrated that removal of the tonsils resulted in relief and cure of the neuritis. In 20 cases carious teeth were found, but in only 6 instances was pain relieved after their removal. Acute or chronic sinus disease was found in 12 cases; prostatitis was present in 8 cases.

The relation of these foci of infection to the neuritis is difficult to evaluate. It is impossible to say absolutely that the removal of the infected foci resulted in the cure of the sciatic neuritis. Yet the conclusion is inescapable that in the cases relieved by removal of tonsils or teeth the recovery was quick in most cases following their removal and in some instances dramatic.

The incidence of other factors was not as high as that of foci of infection. In 17 cases osteoarthritis of the sacro-iliac joints or of the lumbar vertebræ was found. Whether the arthritis was sufficient to cause the sciatic pain is at least open to discussion. In only 2 cases was sacralization noted, and in only 2 was osteoarthritis of the hip discovered.

Diagnosis. The diagnosis of sciatic neuritis and its differentiation from secondary sciatica is not difficult. The cases of sciatic neuritis are characterized invariably by tenderness of the nerve trunks and usually also by tenderness of the muscles of the thigh and calf. Nerve trunk tenderness particularly in the sciatic notch and popliteal spaces was present in some degree in every case in our series; muscle tenderness was found in only 8 instances. The degree of nerve tenderness varies greatly, in some cases being pronounced, the others less severe; but it is always present. Severe nerve tenderness was found in 22 cases, moderate in 24, and mild nerve tenderness in

9 cases. No such tenderness is found along the nerve trunks in secondary sciatic in the majority of cases. It is well known that compression of the sciatic nerve or of any peripheral nerve at a single point may produce tenderness along the nerve trunk at a distance from the point of compression. This is unusual, though it serves to prove that nerve trunk tenderness cannot be invariably interpreted as indicating a primary neuritis. The percentage incidence of such tenderness in cases of secondary sciatica has not been determined in view of its many causes, but its occasional incidence in the secondary form, as compared with its invariable occurrence in primary sciatica, serves but to demonstrate that nerve and muscle tenderness are typical features of the one and an exceptional characteristic of the other.

All other diagnostic criteria of sciatic nerve involvement—weakness or atrophy of the leg muscles, decrease or absence of the Achilles reflex, pain on stretching the sciatic nerve, sensory disturbances and so forth—are as characteristic of one form of sciatica as the other and cannot be used in the differentiation of sciatic neuritis from secondary sciatica. Special signs such as the Lasègue's, Neri's and others, all of which depend on the stretching of the sciatic nerve, are also characteristic of both groups, as would be expected. Laboratory studies are of relatively little value except that evidence of structural disturbances in the vertebræ, pelvis, spinal canal, or muscles indicates a secondary rather than a primary sciatica. Spinal fluid abnormalities such as xanthochromia and increased protein content are characteristic of spinal cord tumor or herniated nucleus pulposus, but increased protein in the spinal fluid may be found in the special forms of neuritis such as the Guillain-Barré syndrome.

In the last analysis the diagnosis of sciatic neuritis as distinct from that of secondary sciatica depends upon the presence of tenderness over the sciatic nerve with or without tenderness of the thigh and leg muscles. In all other physical respects, exclusive of laboratory findings, cases of sciatic neuritis and secondary sciatica are similar.

Discussion. The problem of sciatica is so greatly confused that a review of the more pertinent points under discussion appears to be desirable. Not only is there wide disagreement concerning the cause of the various forms of sciatica, but there is as great divergence concerning their treatment.

Classification. There seems to be general agreement that not all sciaticas can be thrown into a single grouping. This at least is a step in the right direction, for it emphasizes immediately the multiplicity of causes of the sciatic syndrome. Many groupings have been suggested, the simplest and probably most satisfactory being that of Feiling,[9] who divided the sciaticas into: 1, primary or essential sciatica; and 2, secondary or symptomatic sciatica. The cases of secondary sciatica are clear enough; they include all the cases of sciatic pain which can be shown to be secondary to a specific struc-

tural cause of some sort. In the primary group however Feiling includes not only cases of sciatic neuritis which are regarded as cases of true neuritis, but also a large group of cases which he calls sciatic neuralgia, the cause of which is unknown or cannot be determined. These cases have been referred to by others as idiopathic sciatica. The inference that a primary sciatica is an idiopathic sciatica is reflected further by the views of Douthwaite,[7] who divides the sciaticas into primary and secondary, further subdividing the primary group into those of peripheral and those of central origin. He states moreover that no subgroup may be termed primary in the presence of a clearly determinate or specific cause. Here the inference is clear that primary sciatica is sciatica of undetermined origin, the vast majority of which in the opinion of Douthwaite are cases of sciatic neuritis. Chavany[3] divides the sciaticas into true, symptomatic sciatica and pseudosciatica. The further subdivision of the sciaticas into high, middle and low types (Sicard[24]) has some clinical usefulness. Harris[12] refers only to high and low types. High sciaticas are due to lesions of the roots or lumbosacral plexus. Middle sciaticas are the result of lesions of the plexus or of the nerve trunks from the sacrosciatic notch to their entry into the thigh. Low sciaticas are due to involvement of the nerve in the popliteal space.

A classification into primary and secondary sciatica serves all practical purposes, is accurate and at the same time emphasizes the fact that sciatica is variously produced by many causes. The inference that all or some of the primary sciaticas are idiopathic in origin needs further study and will be dealt with under a discussion of the causes of this syndrome.

Causes of Sciatica. There are many causes of sciatica. No useful purpose can be served by an enumeration here of the many conditions which may give rise to the syndrome. It is important however to emphasize the multiplicity of causes of sciatica in order to prevent uniformity in the treatment of a condition which is variously produced.

In the evaluation of the sciatic problem it becomes clear that the cases of sciatic neuritis must be considered quite apart from those of other origin. The fact that no cause can be established for such cases should occasion no greater surprise than for other cases of neuritis, and certainly does not justify their classification as idiopathic. To say that most cases of sciatica are secondary to diseases of the pelvis, vertebræ, or other organs, is not to deny the existence of sciatic neuritis. Evans,[8] for example, reports 40 cases of what he terms primary or idiopathic sciatica. In many cases of sciatic neuritis the precise cause is not disclosed, yet the neuritis cannot be denied. The exquisite muscle and nerve tenderness seen in these cases stamps them as instances of primary neuritis frequently of undetermined origin. In Feiling's clear discussion of the sciatica problem, sciatic neuritis is regarded as a true neuritis the causes of which are uncertain. He discards foci of infection as a vital cause

and says, "I doubt if I can recall a single example out of the many cases of sciatica I have seen when the finding of a septic focus, followed by its appropriate treatment, seems to have affected to any appreciable extent the course of the disease." Our cases do not bear out this belief. In some of them the removal of infected teeth or tonsils appears to have improved the sciatic neuritis greatly, but in many others no such causal relationship could be established. Despite this failure to establish a precise cause in many of the cases of sciatic neuritis, they must nevertheless be regarded as true or primary neuritis, with all the features of a neuritis elewhere in the body. Careful inquiry into bacteriatoxic, metabolic chemical, virus, or nutritional causes may reveal no definite cause for the neuritis, but the same is true of other forms of neuritis as well. Despite all efforts to establish it, there is often no indication of the exact cause of a neuritis involving other parts of the body. For many cases, such a cause can be determined, but for many others it is not clear. Yet no recourse is taken to the term idiopathic neuritis and there seems no real justification for the term in relation to sciatic neuritis. In some instances, as Lichtman[16] has pointed out, sciatic neuritis may be the precursor of hepatic insufficiency, and may be an early manifestation of a disease process which may lead to hepatic disease and hepatic insufficiency.

It is precisely this ignorance of the origin of sciatic neuritis which has led many to assume that such cases are few in number and that those which do exist are often of a secondary type. Hence the inference by Danforth and Wilson,[6] that what is regarded by neurologists as sciatic neuritis is in reality secondary to disease of the lower lumbar spine or sacro-iliac joints, the neuritis being regarded as a secondary manifestation. Hence also the increasing emphasis on the secondary causes of sciatica, all of which represents, of course, a healthy outlook, but adds nothing to our knowledge of primary sciatic neuritis. It tends rather to tip the balance in favor of looking for secondary causes when they are not present, even to the performance of operative procedures. Thus, Williams[28] reports changes in the bones of joints in 94% of 107 cases of sciatica. MacKinnon[20] asserts that all the features of idiopathic sciatica are due to an infectious lumbosacral arthritis. Involvement of the fifth lumbar root in its foramen by infection or arthritis is regarded by Danforth and Wilson,[6] Cochrane,[4] Furnrohr[10] and Putti[23] as an important cause of sciatica. Buckley[2] found a predominance of affections of the lumbar and sacral articulations as causes of sciatic pain among 108 cases of sciatica. More recently attention has been directed to herniation of the nucleus pulposus in cases of sciatica.[18,19,25,26]

In spite of the frequent affirmation that sciatica is the result of many causes, there seems to be a persisting tendency to explain different sciatic syndromes by the same cause. For this reason one finds that sciatic neuritis is either denied a place of its own or is regarded as due to some secondary cause such as osteoarthritis of

the spine. It is this fallacy which must be averted in a consideration of sciatica cases.

Pathogenesis of Sciatic Pain. The origin of the sciatic pain varies, of course with its cause; but here too the assumption is frequently made that most if not all cases of sciatica can be explained by a single pathogenetic mechanism. Some believe that sciatica is related to various forms of neuritic disease.[27] That it is in some instances a true neuritis cannot be denied, though plausible explanation may be found to the nerve tenderness and pain. Harris believes that the neuritis in such cases is a perineuritis of the sciatic sheath in the region of the sciatic notch where the nerve escapes from the pelvis into the buttock.

The concept of a neuritis satisfies relatively few cases however, and obviously can apply only to the small group of primary sciaticas. Hence, other explanations for the sciatic pain have been sought. It is clear that no difficulty is offered by cases of sciatic pain with an obvious structural deformity such as a spinal cord tumor, herniated nucleus pulposus with compression of the lumbosacral roots, pelvic tumor with compression of the lumbosacral plexus, Pott's disease, or other lesions too numerous to mention, with obvious reasons for the sciatic pain. The difficulty lies in explaining the cause of the pain in many cases which have been erroneously regarded as neuritis or have been carelessly regarded as the result of sacro-iliac strain or arthritis or lumbar arthritis, when no evidence for such a background has been demonstrable. For such cases Danforth and Wilson after a careful study of cadavers have offered the explanation that the sciatic pain is due to an inflammatory process of arthritic or traumatic origin causing irritation of the fourth and fifth lumbar roots. Their studies revealed that the intervertebral foramina of the lumbar roots vary in size and that the largest lumbar root, the fifth, is enclosed in the smallest canal and therefore easily susceptible to compression by encroachment. Their clinical studies support their ideas, but it may be objected that the pain of sciatica is frequently outside the nerve distribution of the fifth lumbar root and that it is frequently not a root pain. The concept has received wide support especially from orthopedists.[13,28]

That this idea does not satisfy all the conditions found in all the cases of this group is shown by the contention of Ober,[22] who maintains that many cases of so-called sacro-iliac strain with low back pain and sometimes with sciatic pain are the result of a tight iliotibial band. Severe sciatica, according to Ober, is often associated with the condition. A concept somewhat allied to this is that of Nutter,[21] who believes that sciatica is sometimes due to unusual fascial bands or fascial thickening around the sciatic nerve in the neighborhoods of the sciatic notch. He points out two areas of thickening of the fascia: 1, at the upper border of the piriformis where this muscle is contiguous with the lower edges of the gluteus medius and minimus, and, 2, at the lower border of the piriformis immediately lateral to the great sciatic nerve. Nutter[21] believes that

when the intervals between the muscles are greater than normal, fascial bands may focus. Of 10 cases, 4 were cured by exploration, but none of these showed evidence of fascial bands.

The conception of Bruce,[1] that sciatica is due to an affection of the hip joint, has found little support, though Bruce found 48% of 676 cases of sciatica with evidence of rheumatism or gout. His theory is based on his observations that wasting of the hip muscles is very decided in nearly all cases of sciatica, and on the further observation that there is tenderness on pressure over the capsule of the hip joint. Similarly, an attempt to explain the obscure cases of sciatica by invoking sacro-iliac disease has not succeeded in the absence of evidence of such disease, though Hertzler[14] claims that sciatica is due to a synovitis of the sacro-iliac joint and that the sciatica is due to an irritation of the nerve by the joint inflammation.

A purely muscular origin of the pain in sciatica is offered by Helweg,[13] who found in the majority of 750 cases changes in the muscles of the gluteal region and the back of the leg. All these cases showed nerve tenderness and positive leg-raising signs; whereas cases with pain in the leg without these signs failed to show the muscle changes which Helweg emphasized. He therefore placed in a special group the cases with pain in the leg, muscle changes, and positive leg-raising and nerve tenderness signs. He regarded the firmer consistency of the muscles of the gluteal and thigh regions in these cases as due to a myopathy, characterized by an increased firmness of the muscles to palpation. This myopathy he regards as the result of an "intense and long-continued use of just those muscles or parts of muscles which the palpation examination show to be the seat of the myopathy." Helweg believes that in cases which develop sciatica and therefore myopathy, unusual demands are made on the muscles in question. Even in cases of sciatica due to bone disease he maintains that the muscle disturbance is the primary cause of the pain. The disturbance in the Achilles reflex is due to the accumulation of fatigue substances. Janssen[15] objects that the theory does not explain the tenderness of the nerve trunk, and that the muscles have never been examined directly.

Opposed to this view is that of Lindstedt,[17] that sciatica in the majority of cases is a pure neuralgia without anatomic findings in the nerve, and that it arises from irritating conditions in the periphery of the nerve which cause pain radiating into the whole of the sciatic area.

Summary. The concept that primary sciatic neuritis is rare is not supported by the evidence. We report 55 such hospitalized cases, all of which were severe. It is quite probable that many more cases of sciatic neuritis are seen in general practice, which recover without hospitalization. It is important that this fact be borne in mind in view of the present-day tendency to regard most cases of sciatic pain as being of secondary origin. While cases of secondary sciatica very probably outnumber the primary cases, our experience leads us to the conclusion that true sciatic neuritis is not a rarity. There

appears to be no justification moreover for the concept of an idiopathic sciatica any more than for other forms of neuritis. The causes of sciatic neuritis are those of neuritis in general and those cases for which no cause is found should not be regarded as idiopathic.

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A NEW TEST OF LIVER FUNCTION—THE TYROSINE TOLERANCE TEST

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Abnormalities in the metabolism of tyrosine in the presence of liver disease have long been recognized, but of the many liver function tests employed clinically none has been designed to test the ability of the liver to metabolize this important amino acid. This lack is principally due to the fact that, up to the present time, no reliable quantitative method for the determination of blood tyrosine has been described. The purposes of the present communication are chiefly to describe a quantitative method of blood tyrosine determination, to present a curve of tyrosine tolerance in normal

subjects, and to demonstrate changes occurring in certain types of liver disease. Correlation of its sensitivity, as compared to other tests of liver function, has been made whenever possible.

Impairment in amino acid metabolism in hepatic disease was probably suggested first by Frerichs,[1] who noted the presence of tyrosine and leucine crystals in the urine in cases of acute yellow atrophy. Lichtman,[5] using a quantitative analysis for tyrosine in urine, further observed an increased tyrosinuria in various types of liver disease. Jankelson,[3,4] who employed a qualitative method of tyrosine analysis, was unable to demonstrate the presence of tyrosine in normal blood but found various levels of tyrosinemia in a high percentage of patients with liver disease.

These observations of tyrosine metabolism suggest that a tyrosine tolerance test may be of value in the diagnosis of liver disease.

Methods. *Determination of Blood Tyrosyl.* A modification of the Millon reaction, using the photoelectric colorimeter, was found suitable for blood tyrosyl. The Millon reaction is not specific for tyrosine but is specific for the characteristic phenol group of tyrosine. The term "tyrosyl" refers to the tyrosine and closely related metabolic products which give the test. Spectrophotometric analysis shows that the color produced in blood filtrates is the same as the color produced in pure tyrosine solutions, indicating that metabolic changes in the side chain of tyrosine have little, if any, effect upon the color produced by the reaction. A photoelectric colorimeter is necessary because the color produced by the normal concentration of blood tyrosyl is not intense enough to be easily compared in the visual colorimeter. The Klett-Summerson photoelectric colorimeter was found satisfactory.

Six cc. of blood was drawn and added to dry oxalate (0.15 mg. per cc. of blood). The required amount of filtrate was obtained from 5 cc. of blood. A 1 to 5 blood filtrate was prepared by adding 2 volumes of water, 1 volume of 10% sodium tungstate and 1 volume 1N H_2SO_4 to 1 volume of the oxalated blood, then shaking vigorously and centrifuging. To 7 cc. of the clear centrifugate contained in a centrifuge tube were added 0.5 cc. 7N H_2SO_4, 1.5 cc. 15% $HgSO_4$ in 6N H_2SO_4 and 1 cc. of 0.1N H_2SO_4.* To the standard containing 7 cc. of the same filtrate, 0.5 cc. 7N H_2SO_4 and 1.5 cc. of the mercury reagent were added 1 cc. of tyrosine solution (0.05 mg. in 1 cc. of 0.1N H_2SO_4). The tubes were heated 8 minutes in a boiling water bath, then cooled below room temperature in running water. After adjusting the volume to 10 cc. with water the tubes were centrifugalized and 8 cc. of the clear liquid placed in the colorimeter cell. The blank reading was determined, 0.05 cc. of 5% sodium nitrite solution added, and the mixture shaken. The color produced was read after 4 minutes, using a filter with maximum transmission at 500 mμ. Up to 0.6 mg. of tyrosine added to each cubic centimeter of blood was quantitatively recovered by this method. Duplicate determinations agreed within 3%.

The standard tyrosine solution did not deteriorate for at least 6 months when kept refrigerated.

Calculations. The following calculations are for the Klett-Summerson colorimeter. With other instruments the calculation, although the same in principle, will vary in detail. Three readings were taken: (1) Blank reading of unknown. This reading may be assumed to be the same for the known. (2) Unknown reading. (3) Known reading.

The blank reading (1) is subtracted from (2) and (3), giving the true color value in the 2 tubes.

* For detailed directions for the preparation of the reagents see Folin, O., and Marenzi, A. D.: J. Biol. Chem., **83**, 89, 1929.

True known reading—true unknown reading = k, the color produced by
(3–1) (2–1)
the known added amount of tyrosine.

$$\frac{\text{True unknown reading}}{K} \times \frac{100}{1.4} \times 0.05 = \text{mg. tyrosine equivalent in 100 cc. of blood.}$$

Tyrosine Tolerance Test. Four grams of tyrosine,* 5 gm. of casein and 4 to 5 drops of 1% phenolphthalein solution were placed in 250 cc. of water in a 1 liter Erlenmeyer flask. While the flask was heating over a Bunsen burner, 5N NaOH was added drop by drop and the flask shaken until the tyrosine and casein were in solution and the phenolphthalein color persisted. An excess of NaOH should be avoided. The addition of casein increases the solubility of the tyrosine.

Two drops of oil of peppermint added to the mixture help to disguise the alkaline taste. The flavored solution was well tolerated, even by extremely sick individuals.

The tests were made after an overnight fast, water being allowed until midnight. After withdrawal of a sample of blood the tyrosine solution was administered orally. Blood samples were taken 1, 2 and 3 hours after ingestion of the tyrosine solution.

Other Liver Function Tests. (*a*) *The sodium benzoate conversion test* described by Quick[6] was made by administering 6 gm. of sodium benzoate. Excretion in the urine of less than 3 gm. of hippuric acid in 4 hours is regarded as evidence of hepatic dysfunction.

(*b*) *The Takata-Ara test* was made and interpreted according to the directions of Heath.[2]

(*c*) *Prothrombin Time.* The Quick method[7] was used, and the clotting time obtained was compared with the clotting time of a sample of normal blood which was treated in the same manner.

(*d*) *The bromsulfalein excretion test* was made by injecting 5 mg. of the dye per kilo of body weight. When this dosage is used the normal retention after ½ hour is considered to be from 0 to 10%.

(*e*) *The galactose tolerance test* was made by administering 40 gm. of galactose. Excretion in the urine during a 4-hour period of over 3 gm. of galactose is regarded as evidence of hepatic dysfunction.

Results. *Normal Fasting Level.* The concentration of tyrosyl in the normal fasting subject is equivalent to 1 to 1.8 mg. of tyrosine per 100 cc. of blood. This result is in contrast with the observations of Jankelson[3,4] who found no tyrosyl value in the blood of normal fasting individuals, and this difference in results serves to emphasize the increased sensitivity of the present quantitative method.

Tyrosine Tolerance in Normal Subjects. Administration of 4 gm. of tyrosine to 10 presumably normal subjects yielded the data shown in Table 1.

TABLE 1.—TYROSINE TOLERANCE IN NORMAL SUBJECTS

Sample (hrs. after ingestion of tyrosine)	Blood tyrosyl concentration (mg./100 cc.)		
	Minimum	Maximum	Average
Fasting	1.0	1.8	1.4
1 hr.	4.0	6.4	5.4
2 hrs.	3.6	5.0	4.6
3 hrs.	2.9	4.0	3.4

* Obtained from the S. M. A. Corporation, Chagrin Falls, Ohio.

Tyrosine Tolerance in Liver Disease. After a curve of tolerance to ingested tyrosine in normal subjects was obtained, an attempt was made to apply the test clinically to patients with obvious liver disease and others with suspected liver disease. In some instances of severe hepatic insufficiency, especially advanced cirrhosis, the fasting blood tyrosyl level was significantly elevated beyond the upper normal limit of 1.8 mg. per 100 cc. of whole blood. In 1 instance a fasting level of 4.9 mg. was obtained. In every instance of cirrhosis of the liver thus far studied, the tolerance to orally ingested tyrosine was diminished. In some patients levels as high as 15 mg. were found 1 hour after consumption; furthermore, the hypertyrosinemia persisted at levels as high as 8 to 11 mg. for as long as $3\frac{1}{2}$ hours after ingestion of the substance. This indicates not only an impairment in the ability of the liver to metabolize ingested tyrosine, but shows that the resulting tyrosinemia persists for long periods of time and often remains a permanent part of the abnormal body chemistry comparable to the hyperglycemia of untreated diabetes mellitus.

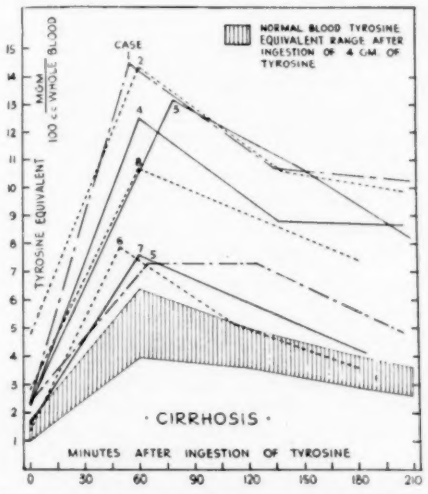

FIG. 1.—Tyrosine tolerance curves in cases of cirrhosis of the liver.

Case Reports. CASE 1. A white woman, aged 44, examined on November 19, 1941, complained of swelling of the abdomen of 5 months' duration. She had been almost constantly inebriated for 3 years following the death of her husband. In July, 1941, she noted onset of mild icterus and gradually increasing ascites. Repeated paracenteses were performed before admission. Anorexia, weakness and chronic dyspepsia had been noted.

Physical examination revealed a pallid, sickly-looking woman with a sallow skin. The abdomen was markedly protuberant; a fluid wave and shifting dullness were present. Six thousand cc. of straw-colored fluid was removed by abdominal paracentesis.

Her blood count revealed 4,090,000 red blood cells per c.mm., 55% hemoglobin per 100 cc. (8.5 gm. by Haden-Hauser) and a volume index of 1.14. Total blood proteins were 5.2%. A bromsulfalein test of liver func-

tion revealed 44% retention of dye in 30 minutes. A Takata-Ara test on ascitic fluid revealed a positive reaction.

A tyrosine tolerance test revealed marked impairment in function (Fig. 1).

CASE 2. A white man, aged 55, first examined on November 15, 1941, complained of vomiting of blood, diarrhea, a loss of 20 pounds in weight, and abdominal swelling. He had been consuming large quantities of alcohol for 8 years. Two months before admission he experienced painless hematemesis and melena. For 4 weeks he had noted swelling of the abdomen. Hematemesis and melena had recurred repeatedly and he was admitted in a semi-stuporous condition.

Physical examination revealed slight icterus of the skin and conjunctivæ. The abdomen was tense with shifting dullness and a palpable fluid wave.

The blood count on admission was 2,400,000 red blood cells per c.mm. with 29% of hemoglobin (4.5 gm. Haden-Hauser) per 100 cc. The blood Takata-Ara test was positive. Total blood proteins measured 5.7%.

The prothrombin time was 34 seconds, as compared to a normal of 16 seconds. The patient improved following three blood transfusions and symptomatic care. The tyrosine tolerance curves obtained is shown in Figure 1.

In the same figure are shown 6 other cases of advanced cirrhosis of the liver. In 6 of these 8 cases, a history of excessive use of alcohol was obtained. In 1 case (Case 7) dinitrophenol had been taken to reduce weight 8 years previously. Hepatomegaly was present in all cases, ascites in 5 and jaundice in 3. The Takata-Ara test was positive in 2 of 3 cases tested. The prothrombin time was delayed in the 4 cases tested, and the oral hippuric acid test was negative in the 1 case receiving this test (Case 3). One individual (Case 5) died 2 days after the test was given. Delayed absorption of the ingested tyrosine seems possible since the character of the response in this instance differed from all the others. This patient presented intense jaundice with an icterus index of 120.

Table 2 compares the results obtained with the tyrosine tolerance test and the percentage of bromsulfalein retention after ½ hour. The icterus indices are included in each case.

TABLE 2.—COMPARISON OF THE PERCENTAGE OF BROMSULFALEIN RETENTION AT THE END OF 30 MINUTES WITH THE PERCENTAGE INCREASE OF BLOOD TYROSINE ABOVE THE MAXIMUM NORMAL VALUES AFTER INGESTION

Cases	Icterus index	Bromsulfalein retention	% blood tyrosine increase over normal maximum value			
			Fasting	1 hour	2 hours	3 hours
1	17	44	30	120	130	160
2	16	Not done	30	100	90	120
3	50	40	30	70	140	140
4	30	48	170	120	130	160
5	120	80	30	10	50	40
6	4	14	−20	20	0	−10
7	4	20	−10	20	20	0
8	6	40	40	70	80	90

Non-cirrhotic Hepatic Disease. The tyrosine tolerance curves obtained in 8 patients with a variety of other abnormalities of the liver or biliary tract but without clinical evidence of cirrhosis are shown in Figure 2.

The first patient (Case 9) had diabetes and a rather marked deficiency state, chiefly in the vitamin B complex. A bromsulfalein test revealed 14% retention of dye. The second patient (Case 10) also had deficiency disease and in addition had rather marked rheumatoid arthritis. A bromsulfalein test in this individual revealed 20% impairment of function. Patients indicated in Curves 11, 13 and 14 had chronic cholecystitis and stones. Two of the

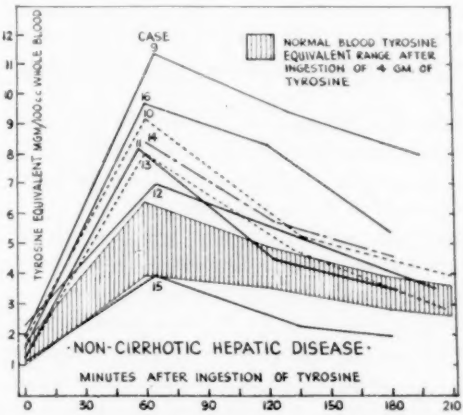
TYROSINE EQUIVALENT MGM/100 CC WHOLE BLOOD
CASE
NORMAL BLOOD TYROSINE EQUIVALENT RANGE AFTER INGESTION OF 4 GM. OF TYROSINE
·NON-CIRRHOTIC HEPATIC DISEASE·
MINUTES AFTER INGESTION OF TYROSINE

FIG. 2.—Tyrosine tolerance curves in cases of non-cirrhotic hepatic disease.

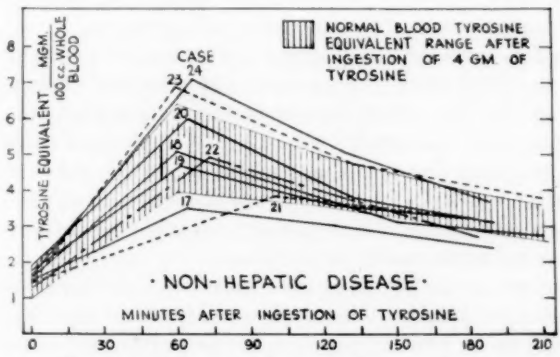
TYROSINE EQUIVALENT MGM. 100 CC WHOLE BLOOD
CASE
NORMAL BLOOD TYROSINE EQUIVALENT RANGE AFTER INGESTION OF 4 GM. OF TYROSINE
·NON-HEPATIC DISEASE·
MINUTES AFTER INGESTION OF TYROSINE

FIG. 3.—Tyrosine tolerance curves in cases on non-hepatic disease

3 tested had normal values by the oral hippuric acid test. One patient (Case 12), at operation, had a carcinoma of the common bile duct and a normal preoperative galactose tolerance test. Case 15 had acute cholecystitis and normal hippuric acid tests on 2 occasions. At operation, the liver appeared normal. The remaining patient (Case 16) had hepatocellular jaundice with icterus index of 80. The galactose tolerance was within normal limits, and the hippuric acid test revealed 58% of normal function.

Non-hepatic Disease. Studies were conducted in a group of patients with a variety of clinical conditions, special emphasis being placed on individuals in whom there was no history nor clinical evidence of liver disease. Three patients (Cases 19, 20 and 24) had chronic gout. One individual (Case 17) had periarthritis and a past history of catarrhal cholangitis. One patient (Case 21) had intermittent claudication and the remaining 2 (Cases 18 and 23) had simple obesity and mild diabetes. There was no evidence of impaired tyrosine tolerance in 6 of the 8 cases studied. The results obtained in Cases 23 and 24 suggest that slight elevations over the normal range of tyrosine tolerance often may occur in non-hepatic disease.

Summary and Conclusions. 1. A reliable method for the quantitative determination of blood tyrosyl had been described, and a normal curve of tyrosine tolerance has been presented, as based on the results obtained in 10 normal subjects.

2. Eight patients with advanced cirrhosis revealed abnormal curves. Other patients with less well-defined liver disease also demonstrated abnormal tyrosine tolerance curves.

3. The results obtained from the test thus far indicate that it is more sensitive than the bromsulfalein and other common tests of liver function. It appears to be reliable, economical, safe and well tolerated. Its sensitivity, as compared to other liver function tests, needs further study, and a final opinion in this regard cannot be made at present. The results show definitely that severe liver disease interferes with the metabolism of tyrosine.

4. Besides yielding information on tyrosine tolerance in liver disease, the present results suggest that valuable information may be obtained by the determination of the fasting blood tyrosyl level in patients with suspected liver disease. Perhaps a simplified test in which only the fasting value and the blood tyrosyl concentration 1 hour after ingestion of tyrosine are determined would give sufficient information from which to draw valuable conclusions concerning functional impairment of the liver.

5. Tyrosine and closely related metabolic products are normal constituents of blood. Their concentrations in the fasting state are equivalent to 1 to 1.8 mg. of tyrosine per 100 cc. of blood.

6. Ingestion of tyrosine by normal subjects causes a prompt rise in blood tyrosyl, which reaches a maximum at the end of about 1 hour; following this there is a gradual fall toward the fasting level.

7. Blood tyrosyl levels may be elevated in the fasting state in patients with certain liver diseases, particularly cirrhosis.

8. The ingestion of tyrosine by patients with cirrhosis of the liver frequently results in markedly elevated blood tyrosyl levels.

9. The present results suggest that the tolerance to tyrosine may prove valuable as a test of the metabolism of tyrosine by the liver and thus serve as a valuable test of liver function.

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FAMILIAL MEDITERRANEAN TARGET–OVAL CELL SYNDROMES

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Target cells are unusually thin erythrocytes which have the appearance of "bull's eyes" or targets in stained blood films, and are unusually resistant to hypotonic solutions of sodium chloride. In 1940, under the designation of "target cell" anemia, I[4] reported the case of a young man of Italian origin who presented a moderately severe hypochromic anemia with numerous target cells, marked splenomegaly, moderate hemolytic icterus and the generalized osteoporotic changes commonly seen in Cooley's erythroblastic anemia. Since no nucleated red cells were present in the peripheral blood, it was believed that the case probably represented an "anerythroblastic" and relatively mild variant of Cooley's erythroblastic anemia. In the latter rather rare condition, which occurs in children of Mediterranean origin (Italian, Greek and Syrian), one of the outstanding features is the presence of numerous nucleated red cells. Marked hypochromic anemia, splenomegaly, generalized bone changes, increased hypotonic resistance of the red cells, and the evidences of increased hemolysis are concomitant features. Death almost invariably occurs before the age of 12, therapy with iron, liver extract and splenectomy being ineffective.[1]

Since but few cases of Cooley's anemia survive to adolescence or the adult state, the mechanism of inheritance has been obscure. A few years ago, Caminopetros[2] found that certain siblings of cases of Cooley's anemia had increased hypotonic resistance of the red cells and suggested that this abnormality might be inherited in a Mendelian recessive fashion. Our studies on this point have revealed mild target cell syndromes in *both* parents and in certain siblings of cases of Cooley's anemia—findings which indicate that Cooley's anemia is definitely inherited, although the exact mode of inheritance remains to be worked out.

* Aided by grants from the Charlton Fund, Tufts College Medical School.

In the paper referred to above,[4] the suggestion was advanced that the fundamental fault in Cooley's anemia might center about the target cell, which indeed might be the inherited defective factor. Further studies, chiefly in Italians have demonstrated that various syndromes presenting among other features target cells and increased hypotonic resistance of the erythrocytes are not uncommon and are usually familial and hereditary. It has been possible to arrange these cases in groups ranging in severity from Cooley's erythroblastic anemia and the previously reported case of target cell anemia to very mild cases of hypochromic anemia with target cells, elliptical and oval cells, and basophilic stippling.

Several of these syndromes (including Cooley's anemia) have already been reported as separate diseases under different headings. These include the following: Familial Hematopoietic Disorder in Italian Adolescents and Adults, Resembling Mediterranean Disease (Thalassanemia) (Wintrobe *et al.*[9]); Familial Microcytic Anemia (Strauss, Daland and Fox[8]); Microcytic, Hypochromic Anemia Associated With Splenomegaly and Refractory to Treatment (Eliel and Bayles[5]); *La Syndrome di Cooley* (*Anemia Mediterranea*) *Nell' Adulto* (Chini[3]); *Anemia ipochromica splenomegalia emolitica con ovalocitosi* (*Ellitocitosi*), *poichilocitosi ed aumento della resistenza osmotica dei globuli rosse* (Introzzi[6]). The possible relationships between these variously described conditions has only occasionally been commented upon and the "common denominator" amongst them has not been well defined.

The present paper presents a preliminary report together with some comments arising from the study of 10 Italian families and of 1 Italian bachelor (comprising altogether more than 50 individuals) all affected with what is believed to be a similar condition, but of varying degrees of intensity. In addition, blood smears of 60 consecutive individuals of Italian origin were examined for oval, target and stippled red cells.

Case Reports. I. *Caruso Family—Hypochromic Anemia, Marked Splenomegaly, Acholuric Jaundice, Marked Bone Changes, Target, Oval, Stippled Red Cells, Increased Hypotonic Resistance.* The patient, a young man of Italian parentage, had been pale since infancy. Physical development had been normal and when examined at the age of 20, he was found to be tall and well formed. There was a suggestive Mongoloid appearance of the face, icterus of the scleræ, moderate pallor, marked splenomegaly, and a rough blowing systolic murmur heard over the entire precordium. A well-defined hypochromic anemia with many target cells was present. Elliptical and stippled red cells were common, but no nucleated red cells were found. The evidences of greatly increased blood destruction were present (bilirubinemia of the "indirect" type, greatly increased output of fecal urobilinogen), together with the bone marrow findings of intense erythroblastic hyperplasia. There were generalized bone changes, quite similar to those seen in Cooley's anemia. The patient's age, normal physical development, and lack of nucleated erythrocytes in the peripheral blood served to differentiate this case from those of typical Cooley's erythroblastic anemia. The patient's family was unusually uncoöperative and it was impossible to do complete studies. However, from the few studies made, a familial abnormality was apparent (Table 5). Although the father,

the mother and one of two sisters studied were apparently in good health, they showed definite numbers of target, oval and stippled red cells.

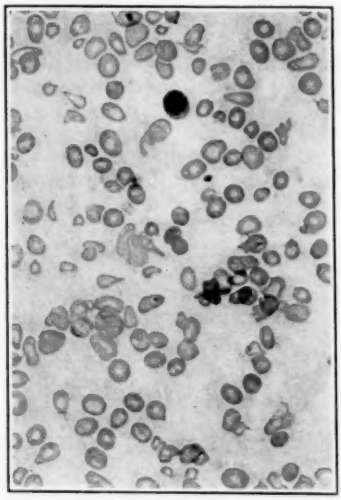

FIG. 1.—Photomicrograph of blood smear (× 520) of a case of outspoken Cooley's anemia (P. W.) prior to splenectomy. There is great diversity in cell size with both microspherocytes and macrocytes, an occasional nucleated red cell and an occasional target cell. The marked evidences of blood destruction were present.

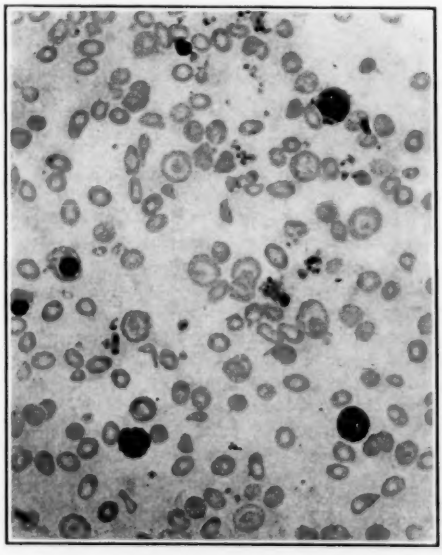

FIG. 2.—Photomicrograph of blood smear (× 520) of a case of Cooley's anemia (P. W.) following splenectomy. The target cells have greatly increased in number, as have the nucleated red cells. In addition there is less spherocytosis and the evidences of increased blood destruction have almost completely disappeared.

TABLE 1.—PERRIELLO FAMILY—HYPOCHROMIC ANEMIA, SPLENOMEGALY, NO BONE CHANGES, ACHOLURIC JAUNDICE, TARGET, OVAL, STIPPLED RED CELLS

		Age	Hgb. (%)	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retics. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./100 cc.)	Spleen	Heart murmurs
Grandfather (mat.)	Dominic Bisesti	81	82	3.79	6,900	470	0.5	105	None	None	None	.44-.12	0.5	..	None
Grandmother (mat.)	Florence Bisesti	53	60	3.56	6,100	341	5.0	90	0.7	5.0	2.5	.42-.20	0.8	Just palpable	None
Mother	Caroline	37	53	4.10	5,200	482	3.0	79	2.9	4.6	1.7	.38-.12	2.7	2-3 f.b.	None
Father	Felix	37	100	5.01	10,500	802	1.0	90	None	None	None	.44-.20	0.9	None	None
Children	Vincent	17	77	4.86	9,100	564	2.4	80	2.0	4.6	1.4	.44-.12	3.5	2 f.b.	
	Mary	15	65	4.89	10,800	724	2.0	80	1.2	1.9	2.1	.40-.16	1.7	1 f.b.	None
	Rose	13	100	5.08	9,000	..	..	104	None	None	..	.42-.24	..	None	Rough systolic and diastolic
	Anthony	11	62	4.47	10,300	653	5.0	80	3.6	1.2	4.1	.36-.12	6.0	1-2 f.b.	Rough systolic
	Phyllis	7	59	4.88	12,000	714	5.3	61	3.4	1.5	4.4	.42-.12	0.7	2 f.b.	Rough systolic
	Edward	6	58	4.40	12,300	616	6.6	73	2.8	1.5	4.3	.42-.16	2.8	2 f.b.	Rough systolic
	Felix	4	60	5.64	13,100	564	2.2	59	4.6	2.3	2.0	.38-.08	0.2	1 f.b.	None
	Dominic	2	74	5.13	11,300	877	2.2	65	0.6	0.4	None	.40-.20	1.7	1 f.b.	None

TABLE 2.—LUCCIO FAMILY—HYPOCHROMIC POLYCYTHEMIA, FREQUENT SPLENOMEGALY, OCCASIONAL JAUNDICE, OCCASIONAL HEART MURMURS, RETICULOCYTOSIS, TARGET, OVAL, AND STIPPLED RED CELLS, NO BONE CHANGES

		Age	Hgb. %	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retics. %	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./ 100 cc.)	Spleen	Heart murmurs
Father	Angelo		Not studied												
Mother	Jennie	53	74	5.49	5,200	467	2.4	71	2.3	2.8	0.5	.38-.08	1.2	4 f.b.	None
Children	Louis	35	Not studied												
	Sarno	31	88	6.01	7,700	..	..	80	1.5	3.9	1.2	.46-.16	1.0	2-3 f.b.	None
	Connie	29	Not studied												
	Rose	27	Not studied												
	Anne	25	Not studied												
	Josephine	23	65	5.14	7,200	494	1.2	70	3.0	1.8	1.0	.38-.08	0.2	Not felt	None
	Antoinetta	22	90	5.76	7,400	549	1.7	74	None	Tendency	None	.44-.26	1.4	Not felt	None
	Agnes	20	62	6.27	8,300	..	..	63	3.5	3.9	0.1	.40-.12	0.6	Not felt	None
	Carmella	18	78	5.64	9,100	..	..	76	3.4	7.1	0.7	.40-.12	0.6	? felt	None
	Mary	16	Not studied												
	Louise	12	Not studied												
Grandchildren (children of Sarno)															
	Richard	7	68	5.45	20,700	872	1.0	70	2.1	2.0	0.5	.36-.08	0.7	3 f.b.	Rough systolic
	Ronald	5	60	5.00	9,000	1500	1.2	68	1.3	2.3	1.0	.40-.12	0.8	Not felt	Rough systolic

II. *Perriello Family—Hypochromic Anemia, Splenomegaly, No Bone Changes, Acholuric Jaundice, Target, Oval, Stippled Red Cells.* This rather large Italian family consisting of father, mother, grandparents, and 8 children was quite coöperative. The mother was referred for study because the diagnosis of congenital hemolytic jaundice had been made in 2 of her children.

In general, the children had developed fairly normally, although 2 were undersized, and 1 was chronically hospitalized for rheumatic heart disease. Three of the children had recently, within a period of 2 weeks, developed nausea, fever, increasing pallor and jaundice. The mother, despite the birth of 8 children in 17 years, considered herself to be in moderately good health, and was able to carry on all the various household duties without assistance.

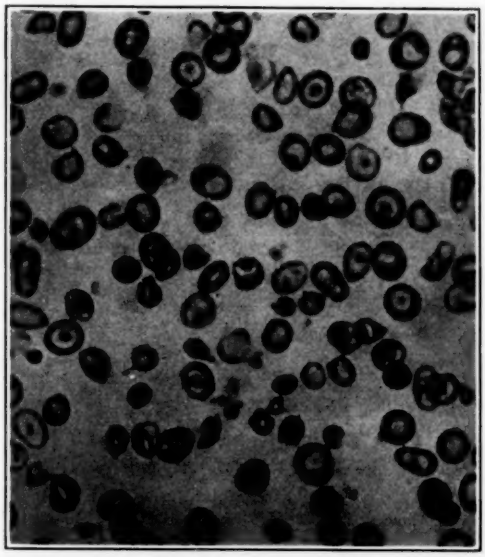

FIG. 3.—Photomicrograph of blood smear (× 560) of a case of severe target cell anemia (J. Caruso) showing many target cells (with central dark spots), much anisocytosis, but no nucleated red cells.

The various physical and hematologic data are arranged in Table 1. Inheritance appeared to be through the grandmother (Bisesti) to the mother, Caroline, both the grandfather and the father being hematologically normal. Slight pallor, slight to moderate splenomegaly, and slight to moderate jaundice were usually present. A Mongoloid appearance of the facies was not apparent. Hypochromic anemia of mild to moderate degree associated frequently with slight acholuric jaundice was present in 7 of the 8 children, although in at least 1 instance (Felix, Jr.) hypochromic "polycythemia" was present. A diminished corpuscular volume, reticulocytosis, increased numbers of target cells, many oval and elliptical cells, and many stippled red cells were present. The resistance of the red cells to hypotonic salt solutions was definitely increased, especially in the "minimal" phase. An increased fecal urobilinogen output (indicating increased blood breakdown) and erythroblastic hyperplasia of the marrow were present in the cases studied. Slight osteoporotic changes, particularly noticeable in the metacarpal bones, were occasionally present. An unusual feature was the presence in 4 of the children (Rose, 13; Anthony,

TABLE 3.—CORRAO FAMILY—HYPOCHROMIC POLYCYTHEMIA WITHOUT ICTERUS, SPLENOMEGALY, OR BONE CHANGES; TARGET CELLS, OVAL CELLS, STIPPLED CELLS, INCREASED RESISTANCE

	Age	Hgb. %	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retics. (%)	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./ 100 cc.
Father	33	88	4.73	7,600	547	1.5	90	None	None	None	.42-.24	
Mother, Marie	31	69	5.95	9,200	612	4.3	60	1.2	4.3	2.2	.42-.12	0.6
Mother's brother, Vincent Blonda	27	82	6.78	10,200	544	1.9	60	5.2	1.2	1.5	.38-.12	1.2
Mother's sister, Josephine Blonda	32	68	5.82	5,100	686	4.1	65	..	..	..	.36-.12	0.3
Loretta	11	68	5.85	11,000	1112	4.0	60	0.9	2.7	0.9	.42-.16	0.7
Rose Marie	9	82	4.21	7,100	568	1.7	97	None	None	None	.42-.22	0.7

TABLE 4(*a*).—VENEZIANO FAMILY—HYPOCHROMIC POLYCYTHEMIA WITHOUT SPLENOMEGALY, HEART MURMURS OR JAUNDICE, MOSTLY ELLIPTICAL AND OVAL CELLS WITH SOME TARGET CELLS

	Age	Hgb. %	R.B.C. (mill.)	W.B.C.	Plates. (thous.)	Retic. %	M.C.V. (c. micra)	Target cells %	Oval cells %	Stippled cells %	Hypotonic fragility (% NaCl)	Bilirubin (mg./ 100 cc.)
Grandmother (Zuffante), Mary	62	74	6.13	16,300	346	..	72	Few	Many	Few		
Grandfather, Joseph	62	96	4.99	7,400	..	..	..	None	None	None		
Mother, Theresa	43	71	5.78	10,600	607	1.3	61	0.5	17.5	1.7	.34-.12	0.8
Father		Not studied										
Children, Vincent	17	74	5.77	6,100	..	..	60	0.9	8.9	0.3	.34-.12	0.2
Armand	6	69	5.76	9,300	..	..	60	1.3	2.8	0.6	.34-.12	0.2

TABLE 4(*b*).—VENEZIANO FAMILY–MARY ZUFFANTE—COURSE OF HEMOGLOBIN AND RED CELL COUNT

Date	Hgb. %	R.B.C. (mill.)	W.B.C.	Platelets (thous.)	M.C.V. (c. micra)
8/22/34	74	6.13	..	346	72
5/ 5/36	80	5.90			
10/ 4/37	82	..	16,300	..	..
1/ 9/39	72	5.57			
3/ 3/40	72	4.97	10,100		
4/24/41	77	4.66			

11; Phyllis, 7; and Edward, 6) of rough, blowing systolic murmurs. Rose had been diagnosed as a case of rheumatic heart disease and was confined to a chronic hospital. In the cases of Anthony, Phyllis, and Edward, who

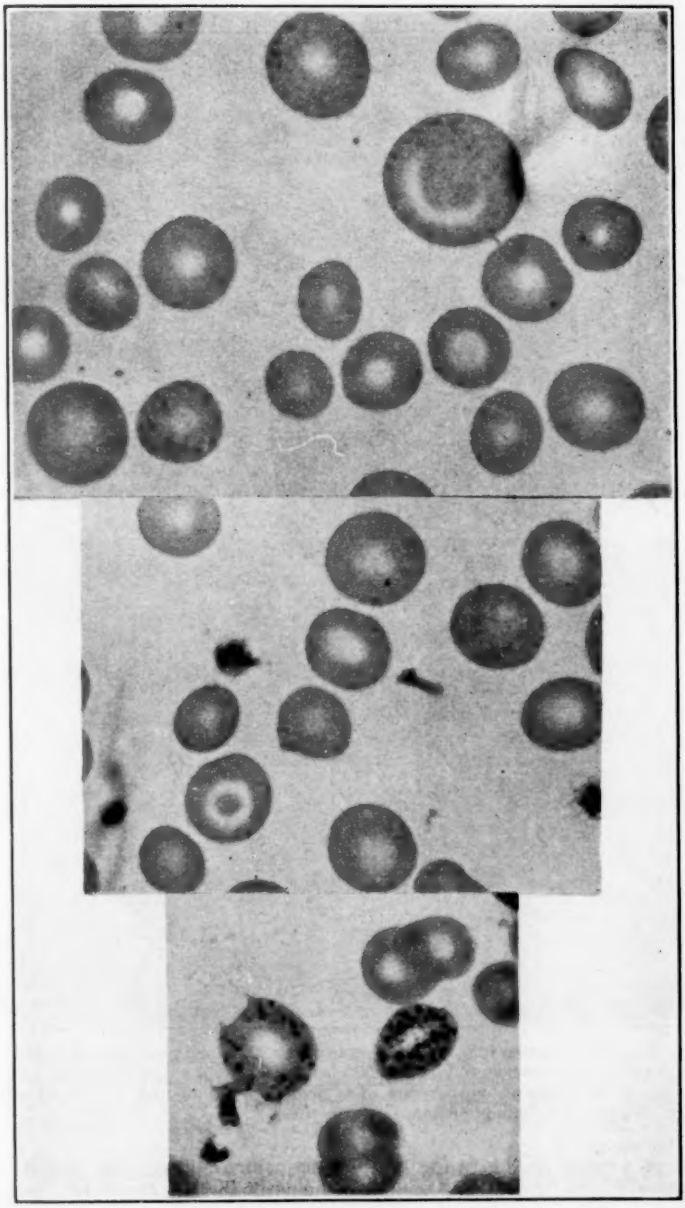

FIG. 4.—Photomicrographs of blood smears (× 2000) of a case of moderately severe target cell anemia (Phyllis Perriello) showing target cells and the very heavily stained stippled red cells characteristic of the condition.

were apparently in excellent good health and gave no history even suggestive of rheumatic fever, loud rough blowing systolic murmurs were present which became accentuated with exercise and did not disappear with change in position. Teleroentgenograms failed to disclose either cardiac enlarge-

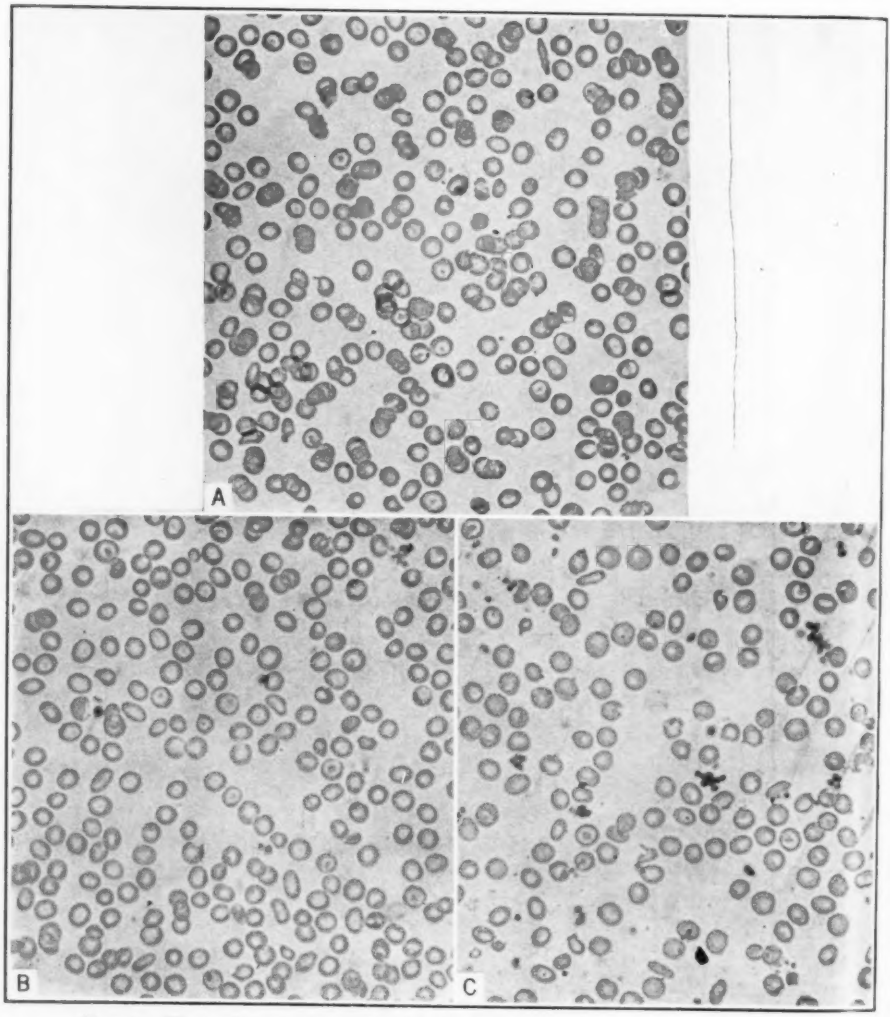

FIG. 5.—Photomicrographs of blood smears (× 520) of cases of "hypochromic polycythemia" with target and oval cells: (*a*) the father of a case of typical Cooley's anemia; (*b*) the sister of another case of typical Cooley's anemia; (*c*) one of a large family (Luccio) with similar hematologic pictures.

ment or a bulge in the region of the pulmonary conus. The hemoglobin values (59%–62%) did not appear sufficiently low to result in "hemic" murmurs. Similar murmurs were found in 2 of the grandchildren of L. family (see below). Treatment with iron, liver extract, vitamin B complex, riboflavin, and spleen extracts was completely ineffective.

III. *L. Family—Hypochromic Polycythemia, Frequent Splenomegaly, Occasional Jaundice, Occasional Heart Murmurs, Reticulocytosis, Target, Oval, and Stippled Red Cells, No Bone Changes.* This large Italian family consisting of mother, father, 11 children and 6 grandchildren was only slightly coöperative, and complete studies could not be made. The mother complained of almost constant headaches, and several of the children complained of "lack of pep" and pallor. In general, however, their development had not been retarded and they considered themselves to be in good health. Three of the children had been treated at one time or another for anemia. Inheritance in this family appeared to be through the mother. Of 5 children studied, 4 were affected. One of the male children (Sarno) had 2 children and both showed the characteristic features of the disease, their mother being completely normal. A Mendelian dominant type of inheritance thus appeared to be present. All of the affected individuals showed a normal physical development and a normal facies without evidence of "mongoloidism." There was slight pallor in several cases, borderline icterus in 2 cases, and splenomegaly in 3 of 8 cases examined. Hema-

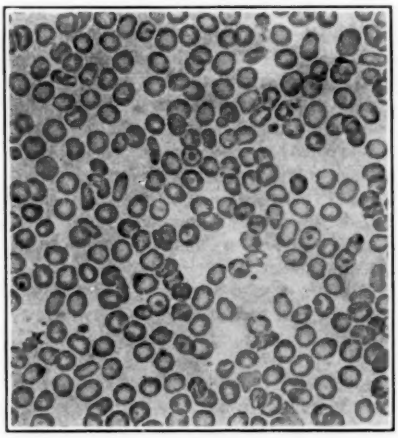

FIG. 6.—Photomicrograph of blood smear from a mild case of hypochromic anemia (Mariello) with target and oval cells.

tologically, "hypochromic polycythemia" (low hemoglobin values in the presence of a high red cell count) was the rule, and was associated with a greatly reduced mean corpuscular volume, slight reticulocytosis, and the presence of target, oval, and stippled red cells (Table 2). No nucleated red cells were seen. Increased hypotonic resistance was a constant finding. Slight bilirubinemia (above 1 mg. per 100 cc.) was present in the mother and 1 of the children (Sarno) had previously had slight jaundice. In 1 of the grandchildren (Richard, aged 7) there was a definite increase in the daily fecal urobilinogen output, indicating increased blood destruction despite the normal blood bilirubin value of 0.7 mg. per 100 cc. Roentgen rays of the skull and of the metacarpal bones in 4 cases were normal. Examinations of the bone marrow were not made. As in the P. family above, 2 of the grandchildren (children of Sarno) showed loud, rough, blowing systolic murmurs heard best in the apical region and along the left border of the sternum, and accentuated with exercise; there was no increase in the size of the cardiac silhouette. Treatment of selected members of the family with large doses of iron liver extract, yeast concentrate tablets, and ribo-

flavin both singly and in combination were completely without effect, the hemoglobin concentration remaining singularly constant from week to week.

IV. *Corrao Family; Veneziano Family; Danubio (cf. also Adorno Family [Cooley's Anemia]—Father and Pauline)—Hypochromic Polycythemia Without Icterus, Splenomegaly, or Bone Changes; Target Cells, Oval Cells, Stippled Cells, Increased Hypotonic Resistance. Corrao Family*—A daughter (Loretta), aged 11, was referred for study of anemia which had been discovered 2 years previously in the course of a routine blood examination prior to tonsillectomy. Despite the continued use of iron therapy during the period of 2 years, no change in hemoglobin had occurred. The child was otherwise quite healthy, although occasionally she became somewhat pale and nauseated. The mother (Marie Blonda Corrao) had always been well except for mild headaches in the past 2 years. A low hemoglobin value had also been discovered in her case 3 years previously while she was in a hospital preparing for a minor gynecologic operation. One of the mother's sisters was known to be anemic and a brother (Vincent Blonda) had recently been told that he had a low hemoglobin value. The father was in good health. One of the mother's maternal uncles, 1 of her maternal aunts, as well as other members of the maternal grandmother's family had been treated for anemia. Study of these cases is now in progress. The mother, who appeared quite healthy, showed fairly numerous telangiectatic blood-vessels over the cheeks. The brother, a strapping young man of 27, seemed in excellent health. Loretta, the patient referred to above, was somewhat sallow but not definitely pale; her sister Rose Marie was healthy in appearance. None of these individuals showed icterus, hepato- or splenomegaly, or cardiac murmurs. However, the blood (Table 3) showed very similar findings of hypochromic polycythemia with target cells, oval cells, stippled cells, reticulocytosis, and increased hypotonic resistance in the mother, her brother and the child Loretta. There was no bilirubinemia. Normal hematologic findings were present in the father and the child Rose Marie. Inheritance was thus dominant and through the mother.

Veneziano Family—Theresa, the mother, aged 43, complained of numerous symptoms (backache, pain in the legs, etc.) and on routine blood examination was found to have a low hemoglobin value, but an elevated red cell count. Her mother was known to be anemic, and her mother's mother had probably been anemic. The patient had been anemic since childhood and because of this a physician in Italy had advised against immigration to this country. At the ages of 18 and 32 she had been treated for anemia with both iron pills and iron injections. With each childbirth anemia was found and she was given iron. The patient's mother and 2 of her 3 children were examined. The mother (Mary Zuffante, aged 62) had been a patient of the Boston Dispensary since 1931 for numerous complaints centering chiefly around the heart and stomach. She was at first considered to have neurasthenia and later "secondary" anemia. Further studies showed low hemoglobin values in association with elevated red cell counts and in 1934 she was thought to have "polycythemia with hypochromic anemia." Treatment with iron caused diarrhea. The hereditary nature of her condition was first noted in 1938 by Dr. H. Brugsch who believed she had "hereditary benign polycythemia with elliptical red cells." In the last year or two there had been increasing cardiac decompensation and a progressive fall in the red cell count from the levels above 6 million to levels below 5 million (Table 4 *b*). The hemoglobin values remained essentially constant.

Of the patient's 3 children, Vincent, aged 15, also had "stomach trouble" for which no cause could be found. Armand felt well. Examination of these individuals was consistently negative, and there was no evidence of anemia, icterus, hepato- or splenomegaly, or cardiac murmurs. The hematologic findings in the patient, her mother, and the 2 children examined were very similar, showing hypochromic polycythemia, very low mean corpuscular volumes, very slight reticulocytosis, and target, oval and stippled red cells with increased hypotonic resistance (Table 4 *a*). Fresh

preparations of the patient's blood showed questionable sickling. Treatment with iron was ineffective. Further studies could not be made because of the family's lack of coöperation.

Danubio—the patient, aged 48, a bachelor, born in Italy, complained of a heavy sensation in the head which had prevented him from working during the past 15 years. He had consulted many physicians and in the course of one study had been found to have "polycythemia," for which phenylhydrazine had been prescribed. With the exception of 1 brother and a nephew, no relatives were available for study. Repeated examinations of the patient showed only numerous telangiectases of the face, the buccal mucous membranes and the nail beds. There was no icterus, hepato- or splenomegaly. The brother and his child showed no abnormalities, either physically or hematologically. Numerous blood examinations gave hemoglobin values of 75%–85%, red cell counts of 6.01 to 6.93 million, slightly elevated leukocyte counts (13,500 to 14,500), normal platelet counts, slight elevation in reticulocytes to approximately 2.0%, very low mean corpuscular volume, no bilirubinemia, and the presence of many target cells with occasional oval and stippled cells and increased hypotonic resistance of the red cells. There were no bone changes; the bone marrow showed erythroblastic hyperplasia. The fecal urobilinogen output and the total blood volume were normal. Treatment with iron, liver extract, and large amounts of spleen extracts were completely without effect on the blood counts and on the patient's symptoms (which were almost certainly neurasthenic in origin).

V. *Mariello Family—Mild Refractory Hypochromic Anemia Without Icterus or Splenomegaly and With Target, Oval, and Stippled Red Cells.* The mother, aged 58, was referred because of hypochromic anemia which had failed to respond to iron. She had but few complaints and physical examination was entirely negative. Although she had 9 children, only 1, Anthony aged 15, was sufficiently coöperative to be examined. He had no complaints and on examination showed no pallor, icterus, hepato- or splenomegaly, or cardiac murmurs. The hematologic findings in mother and son were strikingly similar: slight hypochromic anemia, diminished mean corpuscular volume, and the presence of target, oval, and stippled red cells with increased hypotonic resistance.

VI. *Unselected Italian Individuals.* The blood smears of 60 unselected individuals of Italian parentage who came to the Medical Clinic for various conditions were studied for the presence of target, oval, and stippled cells. In 8 (13%), definite and unequivocal changes in the red cells were apparent. Of these, 3 showed target cells, oval cells, and stippled cells in definite numbers; in 5, ovalocytosis of definite degree was apparent either with or without stippling. Further studies of unselected Italians are being made in the course of which more definitely quantitative values regarding "leptocytosis" and ovalocytosis, etc., will be obtained.

Comment. 1. *The Fundamental Unity of the Various Target Cell Syndromes, Including Cooley's Anemia.* From study of these cases it is possible to arrange in a descending scale, beginning with the outspoken and well-known although rare Cooley's anemia, various more frequently encountered hereditary syndromes, which present as their common denominator a reduction in the hemoglobin level, hypochromia, abnormalities of the red cells including the presence of target cells, oval cells, stippled cells, increased hypotonic resistance and complete refractoriness to iron therapy. At the lower end of the scale are individuals without anemia or evidence of other abnormality but showing increased numbers of target or oval cells (Table 6).

This arrangement of the various syndromes indicates possible relationships among them. That this is probable is indicated by the following: (1) Certain siblings and *both* parents of the cases of Cooley's anemia studied showed the hematologic changes of mild Mediterranean target cell syndrome, usually hypochromic polycythemia. (2) The various groups merged into each other by insensible transitions. (3) Individuals of the same families occasionally showed the same variations as were noted in the groups. These considerations indicate that Cooley's anemia is probably the most severe manifestation of an hereditary disorder occurring in people of Mediterranean origin and in which target cells and increased hypotonic resistance are prominent features.

2. *Heredity.* In the families in which one of the milder syndromes was present, inheritance was present as a simple dominant mechanism, occurring through either parent. This is well brought out in the Periello, Luccio, and Veneziano families, in which members of three generations were available for study. Seven of the 8 Periello children and 4 of the 5 Luccio children studied were affected, although in different degrees. In the Periello family, the transmittor was evidently the grandmother (Bisesti) who showed a very mild condition of hypochromic anemia with elliptical and target cells. Her daughter (the mother Caroline) showed a much more severe condition with jaundice and splenomegaly and the latter's children were similarly affected. The male grandparent and parent were both completely normal. In the Luccio family, the grandmother, the son Sarno, and the latter's children all showed hypochromic polycythemia with target, oval and stippled cells; the grandfather and daughter-in-law were both normal.

In the families of the 4 severe cases studied—3 of typical Cooley's anemia and 1 of the "anerythroblastic" type—*both* the father and the mother showed a mild target-oval cell syndrome. What is more, a mild Mediterranean disorder was often present in certain of the siblings of the cases of Cooley's anemia (Table 5). This suggests that the mild disorder is readily transmitted as a Mendelian dominant, but that the severe disorder requires the presence of homozygous genes. The exact nature of the hereditary process remains to be worked out and will be the subject of another report.

3. *Pathogenesis.* A few comments may be ventured at this time regarding possible pathogenesis. The hypochromia, the very low mean corpuscular volume, and the complete lack of response to iron medication suggest a disturbance in the hemoglobin metabolism, more particularly perhaps in the development of a normal complement of hemoglobin in the cytoplasm of the nucleated red cells in the bone marrow. This may be reflected by the development of unusually thin mature red blood cells (target cells and oval cells). Red cell formation is itself probably undisturbed since there is erythroblastic hyperplasia of a normal (normoblastic) type and the red cell count in the peripheral blood is frequently greater than normal. The presence of large numbers of stippled red cells sug-

gest a possible "toxic" effect on the developing red cell; however, this seems unlikely in view of the hereditary nature of the process, and may be further evidence of an abnormal hemoglobin metabolism. Of particular interest in the more severe cases is the presence of increased hemolysis, of which the cause is at present obscure. This may be due either (1) to an increased breakdown of hemoglobin precursors which cannot properly be metabolized; (2) to a possible increased *in vivo* fragility of the target cell, although *in vitro* it has an increased resistance to hypotonic salt solutions, or (3) to some abnormality in the spleen. Combinations of these factors are also possible. Coincidentally with increased blood destruction are present certain evidences of increased blood regeneration: reticulocytosis, leukocytosis in some cases, and perhaps basophilic stippling. The high red cell counts in many of the cases suggest an attempt on the part of the marrow to compensate for the hemoglobin deficiency. All that can be stated at present is that the disorder—whether mild, moderate, or severe—is an inherited one in which the red cells are abnormally thin ("leptocytosis") and the hemoglobin production abnormal.

TABLE 5.—HEREDITARY NATURE OF 4 SEVERE CASES ("COOLEY'S ANEMIA") IN 4 FAMILIES SHOWING MEDITERRANEAN TARGET OVAL CELL DISEASE

	Hgb.	R.B.C.	Hypotonic fragility	Target cells %	Oval cells %	Type of case
			MERCURIO FAMILY			
Father (John)	85	6.73	.34–.16	0.2	2.5	Hypochromic erythrocytosis with oval cells
Mother (Mary)	84	6.66	.36–.16	0.2	4.6	Hypochromic erythrocytosis with oval cells
John, Jr.	77	5.56	.38–.20	1.0	1.7	Hypochromic erythrocytosis with oval cells
Irene	88	4.98	.42–.24	0.2	0.2	Normal
Helen Marie	*24*	*2.24*	*.38–.16*	*2.4*	*8.4*	*Cooley's anemia*
			WIBBY FAMILY			
Father (Joseph)	85	5.50	.38–.12	8.6	0.9	Hypochromic erythrocytosis with target cells
Mother (Freda)	74	5.40	.36–.08	4.9	0.5	Hypochromic erythrocytosis with target cells
Philip	*21*	*1.77*	*.44–.12*	*1.2*	*5.8*	*Cooley's Anemia*
			ADORNO FAMILY			
Father (Frank)	75	5.24	.40–.16	2.6	1.6	Hypochromic anemia with target and oval cells
Mother (Lucy)	74	4.88	.40–.16	..	..	Hypochromic anemia with target and oval cells
Vincent	*24*	*2.05*	*.36–.04*	*Many*	*Many*	*Cooley's anemia*
Pauline	75	6.20	.38–.12	1.3	2.8	Hypochromic polycythemia
Frank, Jr.	..	..	..	..	..	Normal
			CARUSO FAMILY			
Father (Orazio)	80	4.97	.42–.12	1.3	1.3	Hypochromic anemia with target and oval cells
Mother (Anna)	71	4.29	.38–.12	1.5	0.5	Hypochromic anemia with target and oval cells
Lucy	87	4.36	.42–.16	None	None	Normal
Mary	68	4.72	.38–.12	3.4	1.2	Hypochromic anemia with target and oval cells
Joseph	*50*	*3.12*	*.44–.04*	*32.0*	*Many*	*Anerythroblastic Cooley's anemia —target cell anemia*

4. *Certain Features of Diagnostic Significance.* Study of the cases presented in this paper has indicated that the presence in people of Mediterranean origin (Italians, Greeks, and Syrians) of a low hemoglobin value, a low color index, or a hypochromic type of

polycythemia should immediately bring to mind a possible target cell disorder. In cases of splenomegaly, particularly if they are familial; in cases of possible congenital hemolytic jaundice in Italians; and in various other types of hemolytic syndromes in the same racial group, the question of a target-oval cell syndrome should be thoroughly investigated. The presence of a systolic cardiac murmur in an Italian child may indicate target cell anemia rather than rheumatic heart disease. Likewise, basophilic stippling, when present in an Italian worker exposed to lead, although suggestive of lead poisoning may be indicative of a target cell syndrome; this may occasionally be of medico-legal significance. The diagnosis of sickle cell anemia in a white person of Mediterranean origin should be thoroughly investigated, since occasional cases of target-oval cell syndrome show an unusual degree of elliptocytosis. However, that true cases (transitional forms?) of predominantly African sickle cell anemia occur in Mediterranean individuals is certain.

The diagnosis of one of the target cell syndromes is based upon (*a*) the racial factor, (*b*) a reduction in hemoglobin concentration in association with a low color index, (*c*) refractoriness to iron therapy, (*d*) the presence of increased numbers of target cells and reticulocytes, usually in association with oval and stippled red cells, (*e*) the presence of increased hypotonic *resistance* of the erythrocytes, and (*f*) the absence of such conditions as hepatic disease, steatorrhea, bleeding, or lead poisoning. Target cells and increased hypotonic resistance of the red cells may be present in the two former conditions, which should, however, show the various associated collateral features. In the presence of hypochromic anemia with reticulocytosis, bleeding should always be investigated and may only be found by careful examinations of the stools for occult blood. This is particularly true if the hypochromic anemia does not respond to iron therapy. In certain cases, lead poisoning may have to be ruled out.

A high familial incidence will almost always be found in a given instance if this can be investigated. Whether icterus, splenomegaly, bone changes, cardiac systolic murmurs and nucleated erythrocytes are present depends upon the severity of the condition (*cf.* Table 6). The exact type of syndrome present—whether refractory hypochromic anemia, hypochromic polycythemia, hemolytic target cell jaundice with splenomegaly, etc.—usually depends upon the family affected, since hypochromic polycythemics appear to beget hypochromic polycythemics, unless both parents happen to be affected—in which case a more serious disorder may ensue.

5. *Possible Relationship of the Mediterranean Target Cell Syndrome to the (African) Sickle Cell Syndromes.* An outstanding hematologic feature in a case of sickle cell anemia is the presence of large numbers of target cells. In fact, target cells are frequently more conspicuous in a stained preparation than are sickled cells. Sickle cell anemia, although hemolytic, is almost always accompanied with increased hypotonic resistance of the red cells, particularly in the

"minimal" phase. As with the Mediterranean target-oval cell disease, various gradations in the broad syndrome of sickle cell anemia may be discriminated, ranging from (*a*) the mild "sickle cell trait" brought out only in fresh preparations to (*b*) hypochromic anemia with many target cells and only occasional sickled cells to (*c*) hypochromic anemia with splenomegaly, icterus and frequently cardiac systolic murmurs, and finally to (*d*) the outspoken sickle cell anemia with marked sickling in the peripheral blood, reticulocytosis, stippling, target ovals and nucleated red cells. In such cases, nucleated red cells may be so abundant that the designation "erythroblastic anemia" may be as applicable as in Cooley's anemia.

TABLE 6.—FAMILIAL MEDITERRANEAN TARGET OVAL CELL SYNDROMES

	Anemia	Jaundice	Splenomegaly	Bone changes	Nucleated R.B.C.	Target, oval, stippled cells	Hypotonic fragility	Response to Fe treatment
Cooley's erythroblastic anemia	Severe hypochromic	++	+++	+++	++	+	Incr. resist.	None
"Target cell anemia" (adult erythroblastic type of Cooley's anemia)	Moderate	++	++	++	–	++	Incr. resist.	None
Congenital hemolytic target cell jaundice	Slight to moderate hypochromic	+	+	±	–	++	Incr. resist.	None
Hypochromic polycythemia with splenomegaly and target and oval cells	Hypochromic polycythemia	±	±	–	–	++	Incr. resist.	None
Hypochromic polycythemia with target and oval cells	Hypochromic polycythemia	–	–	–	–	++	Incr. resist.	None
Hypochromic anemia with target, oval, and stippled red cells	Slight hypochromic	–	–	–	–	+	Incr. resist.	None
"Congenital lepto- and elliptocytosis"	None	–	–	–	–	+	Incr. resist.	None

All of these features parallel closely those of the various Mediterranean syndromes. Since the thin target cell is found in both conditions, and since ovalocytosis, elliptocytosis, and meniscocytosis (sickling) may also be indicative of increased thinness, it is possible that the two types of syndromes are closely related. Viewed in this light, various transition forms between the two conditions may be expected.

Recently, Dr. Moises Chediak of Havana informed me of the case of a Cuban family in which 3 children developed a hematologic disturbance. Generations previously, the family, of pure Spanish stock, had emigrated from the Canary Islands. One child developed idiopathic thrombopenic purpura with slow recovery after transfusions. A second child who developed anemia, jaundice, and splenomegaly showed the typical hematologic features of sickle cell anemia although the facies was Mongoloid in type and Roentgen rays of the bones were characteristic of Cooley's anemia. A third child presented hypochromic anemia refractory to iron therapy; after 2 years of observation, sickled cells were noted in wet preparations. The possibility exists that in this family of Mediterranean origin, a transitional condition with the features of both sickle cell anemia and target cell anemia may be present. In an Italian girl

studied at the New Haven Hospital (the records were made available to me through the kindness of Dr. Arthur Geiger) in whom the diagnosis of sickle cell anemia was made, various familial, hematologic, and roentgenologic features of a Mediterranean syndrome of moderate severity were present. Recently, a typical case of Cooley's erythroblastic anemia in a negro child was observed at the Mt. Sinai Hospital of New York. All the various hematologic and bone changes were present and repeated examinations of the blood for sickling were always negative.

Further studies of the possible relationship between these two conditions, one occurring predominantly in Mediterranean peoples and the other in those of African origin, are now in progress.

6. *Terminology.* The matter of terminology for description of these syndromes is a difficult one. Use of the term "target cell anemia" may be criticized because target cells occur in such diverse conditions as hepatic disease, steatorrhea, following splenectomy, and to some extent with chronic hemorrhage. The same criticism may be made for erythroblastic anemia, and for other hematologic conditions which are described by the characteristics of the blood cell. The term Mediterranean anemia, although sufficiently vague, does not adequately describe the cases with a high erythrocyte count, although the hemoglobin level may be distinctly lowered. The numerous previous designations referred to in the introduction are also unsatisfactory for one cause or another. Since most cases occur in Mediterranean peoples and are familial, and since a common feature is the hypotonically resistant target-oval cell, I have thought it best to refer to these cases as "familial Mediterranean target-oval cell disease." This unwieldy term is admittedly unsatisfactory but must await revision as the pathogenic mechanisms are better understood.

7. *Course and Therapy.* Cooley's anemia, the most severe form of the target-oval cell syndromes, is almost uniformly fatal before the age of 12. The milder syndromes appear to run a protracted course without much effect on the general health. In those cases with jaundice and other evidences of increased blood destruction, there may be an enhanced tendency for the development of gall stones; this possibility has not as yet been investigated. The exact significance of the cardiac systolic murmurs heard in a number of the cases, especially in children, is thus far uncertain and must await long-term studies. In 1 of the cases of hypochromic "polycythemia," Mary Z. (Table 4*b*), the course of the anemia during a period of about 7 years from the ages of 55 to 62 could be followed. There was a gradual reduction in the red cell count from 6.13 to 4.66 million, the hemoglobin concentration remaining remarkably constant at between 72% and 82%. This probably indicates a gradual reduction in red cell formation with advancing years. The static quality of the hemoglobin level was noted in all the other cases which were followed.

The response to therapy is uniformly *nil*. Despite the low hemoglobin concentration and low color index, no response whatever to iron therapy occurs. This is about the only exception to the dictum that a hypochromic anemia always responds to iron therapy. Liver extract, various members of the vitamin B complex, splenic extracts, etc., are also completely ineffective. As already stated, the negative results with therapy rule out various deficiency syndromes, and with the hereditary nature of the disease, point to an inherited disturbance either in the hemoglobin metabolism or in red cell formation.

Summary. 1. In a previous paper, attention was directed to a condition tentatively called "target cell" anemia and representing a relatively mild form of Cooley's anemia. The chief hematologic feature was the presence of numerous target cells, which were unusually resistant to hypotonic solutions of sodium chloride.

2. Further studies of Italian families have revealed several syndromes of varying degrees of severity ranging from Cooley's erythroblastic anemia to conditions with mild hypochromic anemia, target, oval and stippled cells, and increased hypotonic resistance of the erythrocytes. These syndromes, inherited usually as a Mendelian dominant, showed a high incidence of transmission in the offspring. In the few cases of Cooley's anemia studied, *both* parents were affected with one of the milder types of syndromes.

3. In a person of Mediterranean (more particularly Italian) origin, the question of target cell anemia should be considered in the presence of splenomegaly, a hemolytic type of icterus, a cardiac systolic murmur, a reduction in hemoglobin, an elevated red cell count, anemia refractory to iron therapy, or stippling or elongation of the red cells. The diagnosis is substantiated by the presence of target, oval, and stippled red cells, increased hypotonic *resistance* of the red cells, and complete refractoriness to iron therapy.

4. The fundamental inherited abnormality appears to lie in a disturbance of the hemoglobin metabolism with the result that the nucleated red cells become deficient in and are likewise unable to take on their normal complement of hemoglobin. In consequence, thin and hypotonically resistant erythrocytes—target and oval cells—are produced. Basophilic stippling and refractoriness to iron therapy are probably concomitant abnormalities. The increased hemolysis in the more severe cases may be due to the breakdown of unused hemoglobin precursors.

5. The numerous resemblances between the essentially Mediterranean target cell syndromes and the essentially African sickle-cell anemia are pointed out. It is possible that the two conditions may be closely related entities with unusual erythrocytic thinness ("leptocytosis") as one of the fundamental abnormal traits. They are important, not only diagnostically, but because the mating of 2 individuals with a relatively mild condition may result in the appearance of either full-blown Cooley's anemia or sickle-cell anemia in the offspring.

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PRIMARY FRIEDLÄNDER PNEUMONIA

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Introduction. The Gram-negative bacillus which now bears his name was discovered by Carl Friedländer[11] in 1882. Friedländer believed that it was the chief cause of pneumonia, while a later opinion held that it was merely a secondary invader, after Sternberg[24] and Weichselbaum[26] showed the pneumococcus to be the most common cause of lobar pneumonia. Now it is known that the Friedländer bacillus is responsible for a small but definite percentage. The large series of Solomon[22] (with review of literature to 1937), Bullowa, Chess and Friedman,[6] Solomon,[23] and Perlman and Bullowa[20] indicate that Friedländer pneumonia is not rare. Solomon emphasized the chronic phase of Friedländer pneumonia and Muschenheim[19] reported 1 patient who, within 3 years had 3 bouts of Friedländer pneumonia with necrosis and cavitation. Friedländer bacilli were present in this patient's sputum for at least 6 years.

The present report is based on 51 cases of Friedländer pneumonia from Bellevue Hospital and The New York Hospital. Five of the chronic cases were previously reported by Solomon,[23] but are included here because of the interesting follow-up observations. The acute and chronic cases are considered together, as separate study of them revealed no significant differences in age or sex incidence, the type of organism involved, blood response, seasonal incidence, the lobes involved, or symptoms. It would appear that acute primary Friedländer pneumonia can terminate with death, with complete fairly rapid recovery, or with parenchymal destruction (the chronic phase). The chronic Friedländer pneumonia is thus an end result rather than a separate entity.

Etiology. Bacteriology. 1. *Morphology.* Excellent bacteriologic descriptions of the short, Gram-negative, non-motile, and non-sporing rods can be found in such textbooks as those of Gay[12] and of Topley and Wilson.[25] The thick capsules are easily stained.

2. *Cultural.* The Friedländer bacillus grows luxuriantly aërobically at 37° C. (range between 12 and 45° C.). Growth on agar is very characteristic, the colonies being large, gray-white, and very mucoid with a glossy, smooth, viscid surface. On a blood agar plate, the colonies are convex, milk-white, 1 mm. in diameter with a smooth surface. There is no hemolysis. Biochemical reactions are varied, because of different strains.

3. *Colony Variation.* As with other bacteria, mucoid, smooth, intermediate rough, and true rough types may be recognized. The mucoid colony (termed "s" or smooth by some workers) is the most important clinically, as this group contains organisms that are antigenic, with the specific soluble substance, and are pathogenic.

4. *Antigenic Structure.* The gummy capsule of the Friedländer bacillus is a nitrogen-free polysaccharide, containing glucose[1,14] and about 92% water. The soluble specific substance of *B. friedländer*, type B, and of pneumococcus type II are closely related chemically. Both are dextrorotary and acidic. Friedländer bacillus, type B, capsular material is precipitated by barium hydroxide and neutral lead acetate, whereas pneumococcus type II capsular substance is not. They are thus not chemically identical, although the two capsular substances must be closely related. Sera of the former will protect mice against pneumococcus type II infection and *vice versa*. Horse sera are superior to rabbit sera in this respect. Heidelberger, Goebel, and Avery[1,14] have suggested that the similar reactions of these two dissimilar organisms must be due to a "closely similar configuration of atoms in some portion of the complex molecule."

Julianelle[16] divided the Friedländer bacilli into 3 serological types, A, B, and C, and a mixture, called X, specificity being based on agglutination, absorption, precipitin, and protection tests. Type specificity depends on capsular polysaccharide as with pneumococci. Later types D and E were described.[22]

5. *Occurrence.* Friedländer bacilli have been found in the soil, air, dust, mud, and water. Experimentally the mouse is the most susceptible laboratory animal. Subcutaneous or intraperitoneal injections of 1:1 million or 1:1 billion dilutions of young cultures often kill mice in 1 to 3 days. In humans, Friedländer bacilli have been isolated from the respiratory tract, stools, urine, bile, meninges, vagina, and uterus.[2]

ETIOLOGIC FACTORS. 1. *Age.* Friedländer pneumonia is most likely to be found in males over 40 years of age (Table 1). Forty-five (88%) of the present series were between 41 and 84 years of age.

TABLE 1.—AGE INCIDENCE OF FRIEDLÄNDER PNEUMONIA

Age of patient, yrs.	No. of patients	Percentage	
21–30	1	2	
31–40	5	10	
41–50	14	27	88 (over 40)
51–60	18	35	
61–70	10	20	
71–	3	6	

2. *Sex.* There were 43 males and 8 females, a ratio of more than 5:1 (Table 2):

TABLE 2.—AGE AND SEX INCIDENCE

Reported series	Total patients	Patients over 40 years		Sex		Ratio Male/female
		No.	%	male	female	
Solomon, 1937[4]	32	28	87.5	28	4	7:1
Bullowa, 1937[5]	41	29	70	36	5	7:1
Bullowa, 1941[7]	37	26	70	32	5	6.2:1
Present series	51	45	88	43	8	5.3:1
	161	128	79.5	139	22	6.3:1

3. *Seasonal Incidence.* The month of admission of each patient was tabulated. November and December have the highest incidence. Of the Friedländer pneumonias, 59% had their onset between November 1 and April 30. Solomon's[22] comparable figure was 65%.

4. *Occupation.* This plays no rôle, and both whites and negroes are affected. Many of the patients have been debilitated; others have had preceding upper respiratory infections. Chronic alcoholism is probably a factor. Cold, exposure, malnutrition, foci of infection, trauma were all present occasionally but Friedländer pneumonia usually starts suddenly in previously healthy people.

EPIDEMIOLOGY. 1. *Incidence.* The reported incidence is low because of infrequent sputum cultures, and because the diagnosis is often not borne in mind. The proportion of Friedländer pneumonia among all pneumonias is reported variously as between 0.5% and 5%.[5,6,13,20,22] The proportion is lower in large collected series of all pneumonias.

2. *Carriers.* The incidence of *B. friedländeri* in the normal upper respiratory tract varies greatly in different studies. Bloomfield[5] found this bacillus in 5.8% of normal throats; Bullowa[6] in 2.2% of 855 throats. Cooper found Friedländer bacilli in 1% of normal throats (Solomon[22]) and Etienne, 4%. Harris[21] in more than 500 throat cultures and mouse inoculations at Bellevue found Friedländer bacilli in less than 1% of patients without respiratory disease. The origin of the oft-quoted figure of a carrier rate of 25%[12] cannot be found, and it is difficult to accept this figure with the above findings.

Excepting Zander's large series,[27] which was without adequate bacteriologic study, outbreaks have been small. Kliewe, quoted by Bullowa, *et al.*[6] reported an epidemic of infections of the upper respiratory tract and lungs due to *B. friedländeri* in 11 children who were exposed to a patient with known Friedländer pneumonia. Friedländer pneumonia is apparently less infectious than pneumococcal pneumonia.

Pathology. MORPHOLOGIC. 1. *Acute phase.* The following description is based on 13 autopsies of the 26 patients who died. When death occurred early (within the first 5 days), the pulmonary findings are characterized by the large, heavy, firm lobes, bright red color, and thick, gelatinous, tenacious, reddish-gray alveolar exudate.

Gross examination reveals the pneumonic lobes to be much heavier and larger than normally, non-crepitant, rubbery, firm, and consolidated. They are almost always bright red in color, much less often salmon or gray-colored. The pleura over the involved lobes is almost always roughened, dull, reddened, and covered with a heavy fibrinous exudate.

Section shows congestion, reddish-gray or brick red color, with a smooth (rarely dull) surface. Red and gray mottling is usually present. The alveolar exudate (also seen in the bronchi) is always thick, gummy, tenacious, glairy, mucoid, gelatinous, and reddish-gray or blood-tinged. In fewer than half of the cases, many small (1 to 6 mm.) abscesses with green-gray pus and friable débris can be seen.

Microscopically, the pleuræ are thick and congested, and covered with a heavy fibrinous deposit. There are often many neutrophils in this fibrinous layer. The alveoli are filled with serous or cellular exudate, which varies in quality in different areas of the involved lobes. The exudate may be serous, or may consist mainly of neutrophils, or mainly mononuclears, few large endothelial cells, and red blood cells. There is frequently a fibrinous meshwork in the more cellular areas. Many large clumps of bacilli may be seen within the phagocytes or free in the alveoli. The alveolar septa are destroyed in many areas and there are areas of intra-alveolar hemorrhages. The interlobar and intercinar septa are thickened and greatly enlarged. Postmortem cultures, shortly after death, yield Friedländer bacilli.

2. *Chronic Phase.* The main process is destruction of the parenchyma with abscess formation. One or more large cavities may be found. There is yellow pus, necrotic tissue, and coarse trabeculation of the abscess wall. Around the abscess is a pneumonitis of variable degree. Microscopically, there is cavitation, parenchymal destruction, much pus and débris without epithelialization of the cavity wall. Interlobular septa are thickened, and there is an infiltration of neutrophils and mononuclears around the abscess. The pleura is thickened and fibrotic.

Other Findings at Autopsy. Empyema, pericarditis, and meningitis each occurred twice. Of interest is the finding histologically, of portal cirrhosis in 4 patients (31%) and fatty liver in 5 patients (38%). One patient had both portal cirrhosis and extensive fatty infiltration of the liver. Spain[21] found the incidence of portal cirrhosis to be about 6% of more than 3000 autopsies at Bellevue Hospital. Solomon[23] noted that "the association between cirrhosis of the liver and Friedländer infection is not uncommon."

Lobes Involved. Among the 51 patients, the right upper lobe of the lung was involved in 23 patients; the right middle lobe in 18; the right lower in 21; the left lower in 22; and the left upper in 19 patients. It can be seen that there is no preponderance of any one lobe.

TABLE 3.—DATA OF 51 PATIENTS WITH FRIEDLÄNDER PNEUMONIA

Case	Age	Sex	Sputum character	Organism in sputum	Blood culture	Lobes involved	Associated diseases	Day therapy started	Day of death	Days of treatment	Onset, treatment, clinical course, complications
1. G. M.	67	M	Rusty	FBA	Pos. (750 colonies)	RUL RML RLL	Arteriosclerosis	9	10	½	Sick 9 days before adm.; ac., fulminating course; aut.: FBA pneum., ac. splenitis, cong. of liver, myocard. fibrosis
2. W. M.	60	M	Pink to red	FBA	Pos.	LLL LUL RUL RML RLL	Portal cirrh., malnutrition, dehydration, arteriosclerosis	11	13	2	Ill at home 10 days; ac. fulminating course; prontosil without effect; aut.: pneumonia of 5 lobes, encaps. empyema LUL, ac. pericarditis
3. N. K.	58	M	Bloody red	FB	None	RUL RLL LUL LLL	Portal cirrhosis, arteriosclerosis	None	..	..	Ac. fulminating course; death in 4 hours; lung culture—F.B.; aut.: pneumonia, portal cirrhosis; interstitial pancreatitis
4. R. M.	65	F	Dark, bloody; thick	FBA	None	LLL LUL	Diabetes mellitus	None	..	..	Grad. downhill course of suppur. pneumonia; repeat. neg. sputa for AFB; bronchoscopy neg.; died at home after 3 months.
5. A. C.	55	F	Thick, tenacious, bloody	FB	Neg.	RUL RML RLL	.....	None	..	..	Ac. fulminating course; death within 24 hours
6. M. P.	56	M	Thick, brownish	FB	?	LLL	.....	None	..	..	Ac. fulminating; death in 20 hours.
7. J. S.	61	M	Small amount; mucoid	FBA	None	RUL LLL	Pulm. fibrosis	None	..	..	Grad. improvement over 4 months; sputa repeated. neg. for AFB; lung puncture and duodenal bile revealed FBA
8. J. McG.	62	M	Copious, dark brown, prune-juice	FBA	Pos.	RUL	Chr. alcoholism	3	33	12	Ac. ill; SP caused irreg. response; foul, yellow sputum; Roentgen ray revealed large abscess; aut.: P.M. cultures of lung, abscess, and bile pos. for FBA; large abscess RUL; purul. bronchitis; fatty liver
9. D. O'C.	52	M	?	FBA	Pos.	LLL RUL	Emphysema	None	.	.	Ac. course; death in 7 hours; coma with meningitis; FBA in CSF.; aut.: P.M. cultures of lung, meninges, spleen pos. for FBA; pneumonia; purulent meningitis
10. [illegible]	[illegible]	M	Bloody; small hemoptysis	FBA	Neg.	LUL	.....	1	..	4	Ac. ill; SP with good response; prompt resolution; Roentgen rays; sputa neg. for AFB
11. J. T.	40	M	Tenacious, bloody; mucopurulent	FB	Neg.	LLL	Sinusitis, pharyngitis	1	..	3	Devel. pneumonia on ward; acutely ill; good resp. to SP (nor. temp. in 24 hours)
12. M. F.	87	M	None	FB	Neg.	RUL	Artscler. heart disease;	2		3	Elderly; comatose on adm.; incontinent; given ST

9. D. O'C.	52	M	?	FBA	Pos.	LLL RUL	Emphysema	None	..		liver Ac. course; death in 7 hours; coma with meningitis; FBA in CSF.; aut.: P.M. cultures of lung, meninges, spleen pos. for FBA; pneumonia; purulent meningitis
10. J. E.	39	M	Bloody; small hemoptysis	FBA	Neg.	LUL	.....	1	..	4	Ac. ill; SP with good response; prompt resolution, Roentgen rays; sputa neg. for AFB
11. J. T.	40	M	Tenacious, bloody; mucopurulent	FB	Neg.	LLL	Sinusitis, pharyngitis	1	..	3	Devel. pneumonia on ward; acutely ill; good resp. to SP (nor. temp. in 24 hours)
12. M. F.	87	M	None	FB (throat)	Neg.	RUL RML RLL	Artscler. heart disease; aur. fibrillation	2	..	3	Elderly; comatose on adm.; incontinent; given ST and NaSP without resp.; died on 3d hospital day
13. N. H.	55	M	Yellow	FBA	Neg.	RUL	Syphilis	..	..	6	Subac. ill; ST and SD without response; RUL abscess cavity cleared markedly in 3 months; left fibrous scar; sputa neg. for AFB
14. E. O'C.	49	M	?	FBA	Pos.	LLL	.....	8	18	7	Ac. ill at home, 7 days; temp. normal 24 hours after SP and NaSP; 4 days later rose to 104°; death
15. R. S.	52	M	Gelatinous; bloody-red	FBA	None	RUL RML	.....	3	..	3	Afebrile in 48 hours after SD; good response; lungs cleared rapidly
16. J. M.	70	M	Small amount; mucoid	FBA	Neg.	RUL	Artscler. heart disease; aur. fibrillation	..	..	8	Adm. stuporous; no history; ac. ill; moribund for 2 weeks; SD, no noticeable effect; temp. grad. fell to normal in 3 weeks Recovered.
17. L. G.	60	M	Thick, gelatinous, bloody	FB	None	LUL LLL RLL	Malnutrition, dehydration, avitaminosis	None	..	..	Ac. ill; died on 5th day; aut.: Friedländer pneum.; sero-fibrin. pleurisy; fatty liver; coron. sclerosis
18. G. J.	51	M	Watery	FBA	Neg.	RML	Chr. alcoholism, fatty liver	2	11	10	Ac. ill; no response to NaSP; icteric at death; aut.: lung and spleen cultures pos. for FBA; pneumonia; fatty liver; early portal cirrhosis
19. L. B.	58	M	?	FBA	Pos.	RML RLL LLL	.....	2	..	21	Ac. ill; NaSD, 5 days without response; afebrile after 24 hours of NaSP; bile culture neg. for FB; grad. improved; small rt. encaps. pleural effusion.
20. C. R.	72	F	Scant, mucoid	FBA	Neg.	RUL	.....	1	..	7	Ac. ill; afebrile 24 hours after SP started; chest cleared rapidly
21. E. S.	49	M	Blood-tinged; mucopurulent	FB	?	LLL	Pulmonary fibrosis	None	..	..	Subac. course with abscess; sm. spontan. pneumothorax over LUL, which cleared; sputa repeatedly neg. for AFB and pneumococci; grad. recovery
22. P. K.	63	M	Thick, bloody; non-foul	FB	None	LLL LUL	Diab. mellitus, pulm. fibrosis	..	62	10	Subac. ill, 2 weeks before adm.; ST no effect; became afebrile 24 hours after SP, but became toxic, weaker, and went downhill; sputa neg. for AFB
23. E. M.	47	F	Thick, yellow	FBA	Neg.	LUL LLL	.....	..	..	..	Had empyema and chest wall abscess; FBA from both; thoracotomy and SP; grad. improved; thoracotomy fistula healed; sputa neg. for AFB
24. A. G.	50	M	Scanty, salmon-colored	FBA	Pos.	RUL	Chr. alcoholism, treated lues	6	..	21	Acu. ill; SF and prontylin without temp. response, but grad. improved; residual RUL cavity; LLL pneumococcal type I pneumonia with bacteremia in 1940 with good response to SP; No FB or AFB in sputum

For key to abbreviations, see footnote, page 667.

TABLE 3.—DATA OF 51 PATIENTS WITH FRIEDLÄNDER PNEUMONIA.—(*Continued*)

Case	Age	Sex	Sputum character	Organism in sputum	Blood culture	Lobes involved	Associated diseases	Day therapy started	Day of death	Days of treatment	Onset, treatment, clinical course, complications
25. A. B.	59	F	Thick, tenacious, bloody, rusty	FB	Neg.	LUL LLL	Bronchial asthma	2	..	21	Ac. ill; given SD and ST; no marked effect; grad. improved after 2 weeks
26. A. L.	47	M	Thick; bloody	FB	Pos.	RML RLL LLL	Morphine addiction, malnutrition	None	..	..	Chr. and ac. ill; died shortly after adm.; aut.: Friedlander pneum.; massive gangrene and multiple abscesses of lung; early portal cirrhosis
27. L. M.	65	M	Mucopurulent; brown	FB	Pos.	RUL RML RLL	Diabetes mellitus	..	..	..	Ac. ill; comatose; neck rigidity; FB in CSF; meningitis Died.
28. P. O'D.	71	M	Scanty; mucoid	FB	?	RUL LUL	Chr. alcoholism, portal cirrhosis	None	..	..	Ac. ill; died on 3d day; liver palpable.
29. P. L.	48	M	Thick, bloody	FB	Neg.	LLL	.....	None	..	..	Ac. fulmin. course; death in 24 hours
30. J. T.	42	M	Thick, bloody, tenacious	FBB	Pos.	LUL	Chr. alcoholism, portal cirrhosis	None	..	..	Ac. ill; semicomatose; died on 5th day; aut.: LUL pneum.; left empy.; pur. pericard.; portal cirrhosis
31. J. H.	56	M	Dark brown	FBB	None	RLL	Chronic alcoholism	7	..	9	Ac. ill; after SD temp. fell from 105° to 101° in 24 hrs.; grad. recovery
32. J. K.	40	M	Dark bloody; hemoptysis	FBA	Neg.	RLL RUL	Chr. alcoholism; fatty liver	None	..	..	Ac. fulmin. course; died in 24 hours
33. B. W.	45	M	Thick, bloody; gelatinous; homogeneous	FBA	Pos.	RUL RML RLL	Chr. alcoholism, delirium tremens; fatty liver	None	..	..	Ac. ill: died in several hours after admission
34. C. L.	50	M	Mucoid	FB	Pos.	RUL RML RLL	Chr. alcoholism; fatty liver	..	..	..	Ac. ill; anti-pneumococcus type II serum without effect; died, 3d hospital day; aut.: Friedlander pneum.; fatty liver
35. J. M.	59	M	Mucoid; red; thick	FB	Pos.	LUL LLL	.....	..	..	..	Ac. fulminating course; pre-terminal; death in 6 hours; FB in lung suction
36. J. McG.	69	M	"Loose"	FBB	Neg.	LLL	Cerebral thrombosis	2	..	2	Developed pneum. in hosp.; temp. fell to 100° 24 hours after SP; grad. recovery
37. A. M.	48	M	Bloody; sm. hemoptysis	FB	None	RUL RML RLL	.....	None	..	..	Ac. fulminating course; liver down to umbilicus; death in 48 hours; aut.: P.M. lung culture gave FB; Friedlander pneum.; early abscesses
38. B. B.	67	M	Small hemoptysis	FBA	Neg.	LLL	Prostatic hypertrophy	7		5	Ill 1 week before adm.; given SP with good response; had FBA in urine for 2 years since pneumonia; no FB in sputum after pneumonia
39. J. M.	41	M	Thick, rusty	FBB	Pos.	RUL	Chr. alcoholism, portal	1	8?	11	Ac. ill; fair temp. response to SP, but great grad

36.	J. McG.	69	M	"Loose"	FBB	Neg.	LLL	Cerebral thrombosis	2	..	2	24 hours after SP; grad. recovery
37.	A. M.	48	M	Bloody; sm. hemoptysis	FB	None	RUL RML RLL	.....	None	..	..	Ac. fulminating course; liver down to umbilicus; death in 18 hours; aut.: P.M. lung culture gave FB, Friedländer pneum., early abscesses
38.	B. B.	67	M	Small hemoptysis	FBA	Neg.	LLL	Prostatic hypertrophy	7	..	5	Ill 1 week before adm.; given SP with good response; had FBA in urine for 2 years since pneumonia; no FB in sputum after pneumonia
39.	J. M.	41	M	Thick, rusty, blood-streaked	FBB	Pos.	RUL RML RLL	Chr. alcoholism, portal cirrhosis	1	80	11	Ac. ill; fair temp. response to SP, but went grad. downhill; icterus and ascites with FBB in asc. fluid
40.	M. C.	50	M	Thick, rusty, blood-streaked	FBA	Neg.	RUL RML	Chr. alcoholism, fatty liver	7	..	10	Ac. ill; small hemoptyses and pleurisy; given SP without response; abscess of RUL yielded FBA
41.	G. B.	58	M	Small hemoptysis	FBB	Neg.	LLL LUL	Diabetes mellitus, portal cirrhosis	1	..	9	Developed pneum. on ward, after early neg. chest Roentgen ray; ac. ill; treated with SP, NaSP and 50 cc. anti-FB serum; grad. recovery over 2 months
42.	A. P.	53	M	Thick, blood-streaked	FB	Pos.	RUL RLL	Chr. alcoholism, portal cirrhosis	14	..	9	Described in text
43.	J. A.	53	M	Thick, bloody; tenacious	FBA	Neg.	LUL LLL	.....	6	..	7	Described in text
44.	E. K.	50	F	Thick, rusty; tenacious; sm. hemoptysis	FBA	Neg.	RLL RML LLL	Portal cirrhosis	..	..	..	Ac. ill; pneum. spread while receiving SP; devel. icterus and ascites; mult. lung abscesses drained; pneum. slowly resolved with fibrosis in 4 months
45.	G. B	57	M	Bloody; thick; tenacious	FBB	Pos.	RUL RML	Chronic alcoholism	4	..	9	Described in text
46.	M. C.	67	M	Scant; mucoid	FBB	Pos.	RUL	Chronic alcoholism	1	..	60	Ac. ill; temp. fell grad. over 6 weeks; mult. cavities of of RUL; pt. in hosp. now; FBB in sput. for 2 months
47.	R. G.	43	M	Sm. hemoptysis	FB	Neg.	LUL	.....	None	..	..	Devel. LUL abscess; grad. clearing and fibrosis over 6 months; sputa neg. for AFB
48.	J. M.	51	F	Thick, yellow; blood-streaked	FB	Neg.	LUL	Diabetes mellitus	None	..	..	Ac. ill; LUL abscess with fluid; grad. clearing over 4 months with fibrous scar
49.	B. D.	40	F	None	...	Pos.	RML RLL	Chronic alcoholism, malnutrition	None	..	..	Ac. ill; died, 7 hours; aut.: Friedländer pneum.: fibrin. pleurisy; fatty liver; P.M. cult. of heart, blood, lung pos. for FB
50.	I. R.	37	M	Tenacious; mucopurulent with blood-streaking	FB	Pos.	LUL LLL	.....	None	..	..	Ac. ill, dying in 4 days (before chemotherapy available); aut.: pneum., pur. meningo-encephalitis; P.M. cult. of ht., blood, lung, spleen, pos. for FB
51.	J. D.	23	M	Thick, rusty, bloody	FB	Neg.	RLL	.....	None	..	..	Ac. ill; grad. clearing of pneum. over 6 weeks; sput. neg. for AFB; follow-up 2 years later revealed nor. chest Roentgen ray, nor. bronchograms of RML and RLL

ABBREVIATIONS: FB, Friedländer bacillus; FBA, Friedländer bacillus, type A, etc.; AFB, acid-fast bacilli; SF, sulfanilamide; SP, sulfapyridine; ST, sulfathiazole; SD, sulfadiazine; NaSP, sodium sulfapyridine. Lobes: RUL, right upper lobe; LLL, left lower lobe; LUL, left upper lobe, etc. M, male; F, female; adm., admission; P.M., postmortem; CSF, cerebrospinal fluid.

Cases 23, 24, 39, 40, and 43 correspond to Cases 14, 16, 13, 12, and 15 of Solomon's report.[23] They are re-presented because of the interesting follow-up observations.

Cases 47 through 51 were observed at the New York Hospital.

Bronchoscopic Findings. Seven patients were examined by bronchoscopy during the subacute or chronic phase of their illness. One examination was negative, while the remaining 6 revealed mucus coming from the bronchi of the affected lobes. The bronchial mucosa was noted to be injected in the affected branches.

Clinical Course. *Onset.* As noted by previous observers, the onset of Friedländer pneumonia, like pneumococcal lobar pneumonia, is usually sudden with cough (91% of cases), sputum (90%), chest pain (82%), and chill (58%). Occasionally prodromata of "colds," upper respiratory infections, and cough were present. Rarely vomiting and epigastric pain were the first symptoms. The patient always appeared acutely ill and dyspneic; often cyanotic and febrile. The admission diagnosis was usually "lobar pneumonia."

Temperature. The first day temperature was below 102° F. in 13 patients (26%); between 102.2° and 104° F. in 31 patients (62%); and 104.2° F. or above in 6 cases (12%). Pulse rates always corresponded to the temperature curve. Previous observers have noted that the temperature does not commonly rise above 102° F. This was noted in 50% of Solomon's cases.[22] In the present series, however, 74% of all patients had first day temperatures of 102.2° F. or above, simulating other types of lobar pneumonia. Perlman and Bullowa[20] found that the temperature, pulse, and respiration curves did not differ significantly from those of pneumococcal lobar pneumonia.

Leukocyte Counts. On admission these were tabulated in 4 groups:

Leukocytes	Patients	%
less than 5,000	3	6
5,000 to 11,000	11	24
11,000 to 20,000	20	43
20,000 and above	13	27

Thus it is to be observed, in a patient acutely ill with pneumonia, a normal leukocyte count may be of slight help in arousing suspicion of Friedländer pneumonia. The same phenomenon is often observed in virus pneumonia, and in the aged.

Physical Signs. The physical signs were varied and indistinguishable from those of pneumococcal lobar pneumonia.

Roentgenogram. Kornblum and Collins[18,9] have observed 4 stages, based on serial chest films: (1) primary bronchopneumonia, (2) secondary pseudolobar confluence, (3) necrosis with formation of multiple thin-walled abscess cavities, and (4) the stage of fibrosis and healing. The resemblance of the stage of multiple thin-walled or large abscess cavity to pulmonary tuberculosis has been noted by many observers. During the acute Friedländer pneumonia, the "predominant finding is a massive, dense, usually homogeneous shadow, which was frequently suggestive of fluid."[6] The sequence noted by Kornblum, Collins and others occur in about one-third of the patients (the group entering the chronic phase). Most patients, including those who die, reveal only the dense massive shadow of

consolidation and a few pass from consolidation to resolution, without pulmonary necrosis and abscess formation.

Sputum. The sputum on admission was almost always described as "thick," "bloody," "tenacious," "gelatinous," "small hemoptysis" (see Table 3).

Bacteremia. The bacteremia is usually slight quantitatively. Previous observers have noted the lack of relationship of mortality to bacteremia, but in the present series, the mortality rate of non-bacteremic cases (23%) is lower than that of bacteremic patients (82%).

Table 4 is a compilation of several large reported series of Friedländer pneumonia, including the present.

TABLE 4.—BACTEREMIA AND MORTALITY RATE

	Solomon 1937	Bullowa 1937	Bullowa 1941	Present series	Present series: acute only	Present series: chronic only
Total no. of cases	32	41	37	51	36	15
Deaths	31	34	31	26	23	3
Mortality rate	97%	83%	84%	51%	64%	20%
No. of cases with blood cult.	27	41	37	40	27	13
No. of bacteremic cases	19	27	12	18	14	4
Per cent of bacteremic cases	70%	66%	32%	45%	52%	31%
No. of fatal bacteremic cases	19	25	9	14	12	2
Mortality rates of bacteremic pts.	100%	92%	75%	82%	85%	50%
No. of cases without bacteremia	8	14	25	22	13	9
No. of fatal cases without bacteremia	7	7	22	5	5	0
Mortality rate of non-bactermic cases	87%	50%	88%	23%	40%	–

Course. Acute primary Friedländer pneumonia may lead to early death (one-half of our cases), fairly prompt recovery with resolution of the pulmonary lesion (in about one-sixth of our cases); or parenchymal destruction with necrosis and abscess formation (the chronic phase, which occurred in about one-third of our cases). Table 3 outlines the course of each patient.

Complications. Among this group of 51 patients, at least 15 had clinical evidence of lung abscess. At necropsy, most had parenchymal destruction of variable degree. Meningitis proven by positive cerebrospinal fluid cultures for Friedländer bacilli was found in 2 patients; purulent pericarditis twice; and a small apical spontaneous pneumothorax on the affected side twice. Pleural fluid was present clinically in 8 patients, the fluid being encapsulated and purulent with positive *B. friedländer* cultures in 3 of these. The remaining 5 effusions were clear, serous, and sterile.

A complication not reported previously is the subsequent development of pulmonary tuberculosis. Amberson has repeatedly emphasized the adverse effects of suppurative disease on old and inactive pulmonary tuberculosis. Baum and Amberson[3] have recently reported a series of patients stressing this again. Three of the present group of 51 patients have developed pulmonary tuberculosis.

Case Reports. CASE 43. One patient (J.A.) was included in Solomon's 1940 report as Case 15. He was admitted on June 10, 1939 with a Friedländer type A pneumonia and developed a lung abscess and encapsulated

empyema. Thoracotomy was performed on July 7; subsequently a bronchopleural fistula developed. Cultures of the abscess and empyema pus showed Friedländer bacillus, type A. Recovery was slow, but the patient was able to return home on January 16, 1940, with his patent bronchopleural fistula. Repeated sputa on this admission were negative for acid-fast bacilli. On July 10, 1941, there was a small hemorrhage from the chest wall sinus. He was immediately hospitalized. Two days later, he had a small hemoptysis. Sputa thereafter were repeatedly positive for acid-fast bacilli. Chest films revealed bilateral infiltrations. The old thoracotomy and abscess precluded accurate visualization of the left lung. The patient was transferred to a tuberculosis sanatorium. Follow-up (March, 1942) reveals a persistent left thoracotomy wound with moderate drainage from the residual empyema cavity. On the right, there is a tuberculous cavity, 3 cm. in diameter. Sputum and pus from the left thoracotomy are both positive for acid-fast bacilli. There are no Friedländer bacilli in the sputum at present.

Case 42. A.P., a 53-year-old white male, was ill about 2 weeks before admission on October 8, 1940. His sputum was thick and blood-streaked. Sputum and blood culture yielded Friedländer bacilli. A type XXI pneumococcus was also present in the sputum. He was treated with sulfapyridine and 240,000 units of type XXI anti-pneumococcal serum (rabbit) with no apparent effect. A Francis skin test with SSS of pneumococcus type XXI was negative. Sputum concentrates were negative for acid-fast bacilli at this time. A small right pleural effusion was noted on October 15. This fluid was clear and negative for pyogenic and acid-fast organisms on culture and smear. On November 6, he developed a bronchopleural fistula with empyema. Empyema fluid was positive for acid-fast bacilli. He was transferred to a tuberculosis sanatorium where a thoracotomy was done later. When last seen (March, 1941) he had a bronchocutaneous fistula, mixed tuberculous empyema, and his sputum was positive for acid-fast bacilli.

Case 45. G.B. is still a patient in the hospital. He was admitted on September 9, 1941, after having been ill at home for 4 days. His sputum was mucoid, non-foul, and bloody; two blood cultures yielded Friedländer bacilli, type B. He was treated with sulfathiazole, without any apparent response. On September 17, he was given 200,000 units of anti-pneumococcal type 2 rabbit serum, intravenously, and this was repeated on the following day, without any noticeable effect. The patient was kept in bed. His first 5 sputa concentrates were negative for acid-fast bacilli, but positive sputa were secured on October 21 and 23. Since then, however, repeated sputa concentrates have been negative for acid-fast bacilli. A urine culture yielded Friedländer bacillus, type B, but was negative for acid-fast bacilli. It is believed that small tubercles have been eroded. This patient is being closely observed to see whether clinical pulmonary tuberculosis will develop.

Serial chest films and repeated examination of the concentrated sputum for acid-test bacilli are most important. Prolonged bed rest is indicated.

Diagnosis. The type-picture of Friedländer pneumonia is an acutely ill male over 40 years of age, with a history of sudden onset of cough, chest pain, and chill, with thick bloody sputum or a small hemoptysis, with an initial temperature above 102.2° F., and signs of lobar consolidation. The diagnosis should be considered in all adult cases of pneumonia of unclear etiology. Sputum and blood cultures should always be secured immediately; these may show the characteristic growth in 24 to 48 hours. A Gram stain will reveal the large, Gram-negative bacilli with heavy capsule. Intraperitoneal injection of the sputum into a mouse will cause death within 24

hours, with many Gram-negative encapsulated bacilli in the peritoneal exudate and heart's blood.

Mortality. The mortality rate of the present series is 51%. The mortality rate does not vary significantly with the age of the patient. Disregarding any therapy received, the mortality rate of this group of patients prior to 1939 was 75%; since then, 35%. The mortality rate varied with the number of lobes involved. Thus, it was 26% with unilobar pneumonia; 65% if two or more lobes were involved. There was no significant relationship of the mortality rate to the admission white blood count.

Of the present series, 29 sputa were typed and of these 79% were type A. Julianelle,[16] in a carefully studied group, found that type A was the etiologic agent in 74% of 45 cases of Friedländer pneumonia, and type B in 4% of these cases. Cooper found Friedländer bacillus, type A, in 95% of her cases, and Solomon[22] in the 10 cases whose sputa were typed, found type A in all. Bullowa[6] found type A in 73% of 33 cases in 1937, and in 79% of 37 cases in 1914. There is no significant variation of the mortality rate for types A and B. Table 5 indicates the relationship of type of organism to the sex of the patient. Of 73 typed sputa, the male to female incidence of type A Friedländer pneumonia is almost 10:1; for type B, it is 3:1.

Of those patients who died, 45% did so within 4 hours of admission to the hospital (usually on the 3d to 6th day of illness) and 80% of all deaths occurred within 5 days of hospitalization. The correlation of mortality rate and bacteremia has been discussed above (Table 4). One patient, not included in this series, had both Friedländer bacilli and pneumococcus type XVIII in sputum and blood cultures. Both organisms were recovered in the mouse. The patient died shortly after admission. This is evidently a case of true mixed infection.

Treatment. *Experimental.* Buttle *et al.*[7] showed that sulfanilamide had little effect in treating mice infected with Friedländer bacillus. Bliss *et al.*[4] found that sulfapyridine was slightly more effective than sulfanilamide in prolonging survival of mice infected with Friedländer bacillus, type B. This was also noted by Kolmer and Rule.[17] Feinstone *et al.*,[10] using mice and a strain E of type B Friedländer bacillus, found that sulfanilamide, sulfapyridine, and sulfathiazole revealed practically no demonstrable therapeutic effect. Sulfadiazine, however, had a markedly beneficial effect. Thus, with the same dose of each drug, these workers found a survival rate of 6% for sulfapyridine and 73% for the sulfadiazine-treated mice. Table 6 is an abbreviation of one of their tables.

It must be emphasized that these data are derived from laboratory studies on mice, using a single strain of Friedländer bacillus, type B. Clinical experience does not substantiate this marked therapeutic advantage of sulfadiazine over other sulfonamides in human Friedländer pneumonia. The varied responses to chemotherapy may be explained by the presence of different strains of Friedländer bacilli.

Clinical. The evaluation of therapy in Friedländer pneumonia is very difficult. Solomon[22] reported a mortality rate of 97% among 32 acute cases without chemotherapy. Five of his 32 cases received type A, anti-Friedländer horse serum, but in small amounts; all died. Bullowa, Chess and Friedman[6] had 6 patients who were treated with *B. friedländeri*, type A serum, with 3 recoveries. These 3 patients had negative blood cultures. Of 18 of their patients with Friedländer pneumonia, type A, without any serum therapy, 17 (94%) died; 10 of these had bacteremia. Perlman and Bullowa[20] found sulfanilamide, sulfapyridine, or serum, or combinations of these were of little value. In evaluating mortality tables, patients living long enough to receive therapy and those in whom therapy was of value in prolonging life must be differentiated. One is impressed in reviewing the protocols (Table 3) by the frequent fall of temperature to 99° F. or to normal within 24 to 48 hours after institution of sulfapyridine therapy. Of importance is the time chemotherapy is instituted. In those patients where the day of onset of symptoms and therapy was clear, the mortality rate was 13% when therapy was begun on the 1st day of the pneumonia, and 50% when chemotherapy was begun later. The value of chemotherapy is not clear. However, sulfonamides appear to have some value in human Friedländer pneumonia in the early stages. They probably have little value after suppuration occurs. Further trial of the sulfonamides is clearly indicated.

TABLE 5.—RELATIONSHIP OF TYPE OF FRIEDLÄNDER BACILLUS TO THE SEX OF THE PATIENT

		Bullowa, *et al.* 1937	Perlman and Bullowa, 1941	Present series	Totals
Type A.	M	22	28	19	69
	F	2	1	4	7
Type B.	M	2	4	6	12
	F	0	4	0	4
Untyped.	M	12	–	18	
	F	3	–	4	

TABLE 6.—MICE SURVIVAL AND CHEMOTHERAPY.
(Adapted from Feinstone, Williams, Wolff, Huntingdon, and Crossley.[10])

	No. of mice	Mice surviving	% survival
Sulfanilamide	100	2	2 0
Sulfapyridine	99	6	6 0
Sulfathiazole	100	2	2 0
Sulfadiazine	86	63	73 6
Controls	78	0	0 0

After the patient enters the chronic phase, therapy is conservative. Most patients do well and these lesions go on to complete healing, often with fibrous scars. Patients with chronic lung abscess require a prolonged period of bed rest with serial chest films. The abscesses are non-putrid and do not contain anaërobes, which may explain the tendency to heal. If healing does not occur, the question of thoracotomy arises. None of the present series of patients underwent surgical intervention during the chronic phase. Two

patients (Cases 23 and 44) had thoracotomies with drainage of the acute Friedländer lung abscess. Both did well and went on to healing. The ideal management of the non-healing residual abscess cavity is not clear, as there have been too few cases.

Follow-up observations on 10 patients now living, at varying intervals after their attacks of Friedländer pneumonia, reveal:

Case 13. N.H., 3 months after onset of his pneumonia, still has residual infiltration, parenchymal destruction, and fibrosis but serial films have revealed progressive clearing. Sputum negative for acid-fast bacilli.

Case 19. L.B., 10 months after onset of Friedländer pneumonia is feeling fine and has no complaints. Physical and roentgenographic examinations of the chest are negative.

Case 23. E. M., 2½ years later, still has persistent cough with about 300 cc. mucopurulent sputum. Examination of chest reveals many coarse moist rales with bronchovesicular and bronchial breath sounds over the entire left lung, anteriorly and posteriorly. Bronchograms in May, 1942 reveal bronchiectasis of left upper and lower lobes. Friedländer bacilli, type A, are still present in her sputum. This patient may have had previous bronchiectasis.

Case 24. A. G., 2½ years later has a residual cavity, but feels fine. Sputum negative for acid-fast bacilli and Friedländer bacilli. No cough.

Case 25. A. B., 1 year later feels fine and has no complaints. Physical examination of chest and chest roentgenogram are both negative. Throat culture revealed no Friedländer bacilli.

Case 31. J. H., 3 months later has occasional cough without sputum. He has gained 10 pounds. Examination of chest and chest roentgenogram are both clear. Throat culture is negative for Friedländer bacilli.

Case 36. J. McG. is in a hospital for chronic disease because of his hemiplegia. Friedländer bacilli were present in the sputum for 18 months after his acute pneumonia, but are now absent.

Case 38. B. B., 2 years later feels well. Chest examination and chest film are negative. Urine culture still reveals Friedländer bacilli, type A. Throat swab is negative for Friedländer bacilli.

Case 40. M. C., 3 years later has a chronic cough with occasional blood-streaking. Weight has been stationary. Physical examination of the chest was negative. Chest film revealed thickened, fibrotic interlobar fissure between the right upper and middle lobes. Sputum is negative for Friedländer bacilli.

Case 41. G. B., 2 years later has no complaints. Chest examination and roentgenogram are negative. Sputum culture reveals no Friedländer bacilli.

Summary and Conclusions. 1. Based on the present series of 51 patients with Friedländer pneumonia, 88% of the cases were more than 40 years of age. The ratio of males to females was more than 5 to 1. Almost 60% of all cases occurred in the 5-month period from November 1 to April 30. Occupation played no rôle.

2. The apparent incidence of Friedländer pneumonia at Bellevue Hospital is 1.6% of all pneumonia. The actual incidence is probably higher. The incidence of carriers of *B. friedländeri* is 1% or less, based on recent surveys. Several carriers of *B. friedländeri* have been found to have bronchiectasis. Friedländer pneumonia is less infectious than pneumococcal pneumonia.

3. The morphologic findings at necropsy of the acute Friedländer pneumonic lung have been described.

4. The incidence of fatty degeneration of the liver and portal cirrhosis at necropsy may be higher in patients with Friedländer pneumonia than in the general population. Larger series of cases will be necessary to decide this.

5. All lobes were about equally involved with pneumonia. Bronchoscopies during the chronic phase usually revealed mucopus coming from the bronchi of the affected lobes.

6. The onset of Friedländer pneumonia is sudden with cough (91%), sputum (90%), chest pain (82%), and chill (58%). The patient is usually acutely ill and dyspneic; often cyanotic and febrile. First day temperature of 102.2° F. or above was present in 74% of patients. The admission sputum was described as "thick," "bloody," "gelatinous," or "small hemoptysis."

7. Bacteremia is usually slight quantitatively. Positive blood cultures were present in 45%. The mortality rate for bacteremic patients was 82%; for non-bacteremic patients, 23%.

8. The roentgenogram of the chest usually revealed a dense, homogeneous shadow of consolidation. This was followed by death, or complete resolution within a short period, or pulmonary necrosis which usually went on to fibrosis and healing.

9. Among the complications were meningitis, purulent pericarditis, and small apical spontaneous pneumothorax, each occurring twice (4%). Pleural effusion was present in 8 patients (17%), the fluid being purulent in 3 of these. Pulmonary tuberculosis later developed in 3 patients (of 15 who entered the chronic phase). Serial chest films and repeated examination of sputa concentrates for acid-fast bacilli are most important.

10. Diagnosis is simple if Friedländer pneumonia is borne in mind. Routine cultures of the sputum as well as the blood of all patients with pneumonia is indicated.

11. The gross mortality rate of the present series is 51%. There is no significant variation of the mortality rate for types A and B. Of all deaths, 80% occurred within 5 days of hospitalization.

12. Although some experimental data on mice favor sulfadiazine, a review of the protocols of the present series indicates that sulfapyridine may be the drug of choice in acute Friedländer pneumonia. However, at best, chemotherapy has proved to be only of questionable value in most cases, and a final decision must be withheld at this time. In the chronic phase, the management is conservative and usually non-surgical, as most of these lesions will go to fibrosis and healing.

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INCIDENCE OF BRONCHIAL ASTHMA IN THE WHITE AND NEGRO

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Considerable confusion exists with regard to the relative racial incidence of various diseases although there is a slowly growing literature on the subject. One of the earliest and most comprehensive monographs is that of Matas[8] which consists of a general survey, surgical in nature, of disease incidence in whites and negroes. Since this time a number of articles dealing with some particular phase of the subject have appeared.[2,5,6] A rather thorough inquiry into

the literature has failed to reveal any articles dealing with the incidence of asthma in the negro though Scheppegrell[9] emphasized that colored people were afflicted with hay fever about one-third as often as whites. Indeed it seems to be the general impression that negroes are relatively immune to allergic diseases. It is of passing interest that Hrdlicka,[7] who had extensive experience with American Indians stated that asthma is rare among Southwestern Indians and that no instance of severe asthma was encountered; Coca[3] questioned physicians dealing with Indians whose replies suggested that while the allergic trait is not absent in the Indian race it is very much less marked in the Indian than the white.

Using the data compiled from army experience in the World War I, Davenport and Love[4] classified their cases into total admissions from bronchial asthma; ratio of admissions per thousand; length of hospital stay and mortality rate (see Table 1). Inasmuch as there were many fewer negro than white troops the total values are correspondingly smaller for the former; the relative values are higher however, in every respect. Thus in this selected group of so-called normal males of military age, there was more asthma in negroes than in whites and it was apparently of severer grade as concerned both morbidity and mortality.

TABLE 1.—INCIDENCE OF BRONCHIAL ASTHMA IN WHITES AND NEGROES
(Army Data From World War I)

	White		Negro	
	Total	Ratio/1000	Total	Ratio/1000
Admissions	6,453	1.79	1,017	3.55
Days lost	157,818	.12	20,118	.19
Discharges for disability	2,433	.68	439	1.53
Deaths	24	.01	10	.03

We have been impressed in dealing with large numbers of negro patients at Charity Hospital that bronchial asthma is certainly not rare in the negro. In order to determine whether this clinical impression was correct we turned to the data derived from cases seen at the Charity Hospital of New Orleans over a 5-year period from 1937 through 1942.

Reference to Table 2 will show that in our series asthma is approximately half again as common in the white as in the negro.

TABLE 2.—INCIDENCE OF BRONCHIAL ASTHMA IN WHITES AND NEGROES
(Charity Hospital Cases From July 1, 1937 through June 30, 1942)

	White		Negro	
	Male	Female	Male	Female
Admissions by race and sex	71,393	79,647	59,212	85,272
Number of cases	496	509	239	324
Ratio of admiss. per 1000	6.95	6.39	4.04	3.79
Hospital stay (in days)	9.03	8.34	9.13	8.26
Deaths	38	10	8	8
% deaths	7.66	1.96	3.35	2.47

We were, however, impressed with the fact that the hospital stay was essentially the same in the two races. Our data are paralleled by the findings of Adams[1] who studied a large group of white and colored

workmen. He found that in the respiratory group of diseases the frequency for whites is greater, but that the duration per case is, however, greater for the colored resulting in more time lost per individual by the colored than by the white. He noticed this racial difference in all cases of respiratory diseases. Perhaps this discrepancy is to be explained by the findings of Smillie and Augustine[10] who in a careful study of the vital capacity of the negro race observed that the vital capacity in both sexes and for all age groups studied is markedly lower than the vital capacity of the white race. When calculated from surface area, the difference is 15% to 20% in children and 25% to 35% in adults.

Although it is a clinical impression that few people die of bronchial asthma, and indeed this is borne out by the army experience, there was a number of deaths recorded in our series.

From the army experience, as well as our own, it is concluded that bronchial asthma is a common disease among negroes.

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BLOOD STUDIES IN THE AGED

The Erythrocyte in the Aged Male and Female

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(From the Hospital and Home of the Daughters of Jacob)

In a previous paper from this institution,[18] it was shown that the ascorbic acid state of the aged individual was far from the ideal. In 1930, Mettier, Minot, and Townsend[11] showed that an anemia resulted from a deficiency of vitamin C. These observers further noted that when scorbutic patients showed an anemia, iron and liver therapy produced little or no effect on blood formation; but with an addition of vitamin C to the diet, marked response was obtained. In view of these findings, it was thought of interest to investigate the hematology of the normal aged individual. It was considered of further interest to compare our findings with the "normal" values reported in the literature.

Experimental Procedure. The subjects used in this study comprised 50 males and 50 females. They were all ambulatory, and were housed in the "Home" division of the institution. They gave no clinical evidence of disease, and beyond a slight degree of myofibrosis, were electrocardiographically negative. No individual who gave either clinical or electrocardiographical evidence of coronary disease was used. The usual dietetic regimen was adhered to, and during the 48-hour period preceding this study, they received no medications. The ages of the males ranged from 65 to 91 years, with the average age being 78.3 years, and the ages of the females were from 66 to 104 years, with the mean age at 77.2 years.

Venous blood was withdrawn from the fasting subject by means of a 20-gauge needle. As soon as the needle entered the vein, the tourniquet was removed, and a period of at least 2 minutes was allowed for restoration of normal conditions before removing the blood. Two cc. of blood was removed in each case.

As an anticoagulant, a mixture of 4 parts of ammonium oxalate and 6 parts of potassium oxalate was used, since this mixture does not cause any shrinkage of the blood cells.[19]

Hemoglobin determinations were made in duplicate, using a Sahli type hemoglobinometer, with a 15-minute period being allowed after the addition of the blood to the hydrochloric acid, before reading the results. Weekly determinations, in duplicate, of the blood iron using the method of Wong[30] were made, as a means of checking the hemoglobin.*

Red blood cell counts were made in duplicate, using 2 different pipettes certified by the U. S. Bureau of Standards, on a certified Spencer "Bright-line" hemocytometer. Hayem's solution was used as the diluting fluid.

The volume of packed cells was determined by placing the well-mixed blood in a Sahli hemoglobinometer tube to the 100 mark, and centrifuging at high speed until the maximum packing of the cells took place.[25] The volume of packing was then noted. The percentage relative to the "normal" was calculated by dividing this determined value by the "normal" value of the packed cells, in this case assumed to be at 48.0 cc. for the males,[26] and 46.0 cc. for the females.[23]

The resistance of the red cells to hypotonic salt solutions was determined as follows: Reagent grade sodium chloride was heated over a flame until all the adsorbed moisture was driven off. It was then kept in a desiccator over anhydrous calcium chloride until needed. Exactly 1.0000 gm. was weighed out on an analytical balance, dissolved in distilled water, and made up to 100.0 ml. in a volumetric flask in a water-bath at 20° C. A series of dilutions of saline was next prepared, ranging from 0.5% to 0.2%, in steps of 0.02%. Two cc. of each dilution was placed into each of a set of test tubes properly labeled as to the salt concentration, and a drop of the blood to be tested added to each. At the same time, another set of tubes was prepared as previously, and a drop of blood from a young healthy adult was added to each. Both sets of tubes were well shaken and set aside at room temperature for 2 hours, at the end of which time, the tube in which hemolysis began, and that in which hemolysis was complete was noted. (If the normal blood varied by more than 0.04% from the accepted normal figures of 0.44% for minimal resistance and 0.32% for complete hemolysis[20] the test was repeated using fresh dilutions of saline.)

Reticulocyte counts were done by making blood smears on slides that had been prepared in advance by having a thin film of cresyl blue on them, and counterstaining with diluted Wright's stain.[16] A total of 500 red cells was counted and the percentage showing reticulum noted.

* Where normal values for hemoglobin have been determined by the oxygen-combining capacity of the blood, an assumption is made, namely, that the oxygen-combining power of the blood is 1.34 cc., *i. e.*, 1 gm. of hemoglobin will combine with 1.34 cc. of oxygen at standard conditions. However, this figure has never been determined with certainty, and the value, 1.34, is at best only an approximation.[21] On the other hand, the iron content of the hemoglobin molecule is accurately known.[7] Hence, an analysis of the cells for the iron content gives an extremely accurate method of indirectly measuring the hemoglobin.

With the above technique, hemoglobin values were found ranging from 9.7 gm. per 100 cc, to 15 gm. per 100 cc. for the males, and from 9.5 gm. per 100 cc. to 16 gm. per 100 cc. for the females. The mean hemoglobin concentration for the male group was found to be 12.65 gm. per 100 cc., while the mean value for the females was 11.7 gm. per 100 cc. In computing the percentage hemoglobin, the value 14.5 gm. was used as representing 100% for both sexes.[18] Table 1 shows the distribution of the hemoglobin values for the males, and Table 2 shows the corresponding values for the females. Table 3 presents the absolute and the percentage hemoglobin of the various age groups for both males and females.

The results of red blood cell counts may be found in Tables 1 and 2. Table 3 shows the mean erythrocyte counts for each age group for both sexes, the values ranging from 3.30 millions per c.mm. to 5.09 millions per c.mm. for the males, and from 3.2 millions to 5.21 millions per c.mm. for the females, the average male and female values being 4.42 millions per c.mm. and 4.11 millions per c.mm., respectively.

Volumes of packed cells were obtained ranging from 35 to 52.2 cc. per 100 cc. for males with an average volume of 41.2 cc., and for the females, 26 cc. to 52 cc. per 100 cc., with an average of 36.7 cc. These figures correspond to a percentage of 72.9 to 109 of the "normal," with the average mean value being 85.8%, and from 54 to 113%, with an average of 80% for males and females respectively. The results of these determinations may be found in Tables 1 and 2. The mean values for the various age groups are seen in Table 3.

The results of determinations of the fragility tests may be found in Tables 1 and 2 with the average for each age group in Table 3. The overall mean values for beginning and for complete hemolysis were computed to be 0.45% and 0.33%, respectively, for the males, and 0.42% and 0.35% for the females.

The results of the reticulocyte counts are given in Tables 1 and 2, the average for each age group in Table 3. The mean value for the male group was calculated to be 0.53%, with values ranging from 0.14% to 1.80%, while the mean values for the females was 0.64%, with values from 0.18% to 1.26%.

Computed Constants. The following indices were computed from the experimentally determined values: The color index, volume index, and the saturation index. Computations were also made of the mean corpuscular hemoglobin, mean corpuscular volume, and of the mean corpuscular hemoglobin concentration.

Color Index. This well-known figure expresses the relative amount of hemoglobin in the erythrocyte as compared with "normal" blood. The "normal" values used were a hemoglobin concentration of 14.5 gm. per 100 cc. and a red cell count of 5,000,000 cells per c.mm. for the males, while for the females we used a red cell count of 4,500,000 cells per c.mm., with the same hemoglobin as "normal." The color indices for the male group ranged from 0.92 to 1.05 with an average value of 0.99, as is shown by Table 1. For the female group, the color index ranged from 0.82 to 1.01, the average value being 0.88 as is

shown by Table 2. Table 3 shows the color indices for the various age groups for both sexes.

Volume Index. The volume index is an indication of the average volume of the red cell, relative to the "normal." For the computation, a "normal" packed cell volume of 48 cc. and an erythrocyte count of 5,000,000 cells per c.mm. were used for the males, and for the females, the "normal" packed cell volume was taken to be 46 cc. with a red

TABLE 1.—EXPERIMENTAL AND CALCULATED VALUES FOR GROUP (MALES)

No.	Age	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., $\mu\mu$	Mean corp. Hb., $\gamma\gamma$	Mean corp. Hb. con.	Saturation index	Reticulocytes, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
1	65	11.7	80	4.2	0.99	47.3	98.5	1.04	110.2	27.8	24.8	0.91	0.43	0.44	0.36
2	67	12.3	85	4.4	0.99	42.7	89.1	1.04	100.0	28.1	28.6	0.95	0.22	0.48	0.32
3	68	12.8	88	4.3	1.02	41.0	85.4	0.99	95.5	29.8	31.2	1.03	1.00	0.42	0.30
4	69	14.3	99	5.1	0.99	51.1	106.0	1.06	102.0	28.2	28.1	0.93	0.29	0.40	0.32
5	70	11.4	79	4.1	0.96	37.2	77.5	0.96	90.8	27.8	30.7	1.02	1.18	0.46	0.38
6	72	9.9	68	3.5	0.97	35.0	72.9	1.04	100.0	28.3	28.3	0.93	0.17	0.40	0.28
7	73	13.2	91	4.8	0.95	43.4	90.3	0.94	90.0	27.4	30.2	1.01	0.68	0.42	0.32
8	73	13.6	94	4.8	0.98	47.0	98.0	1.02	98.0	28.3	28.9	0.96	0.63	0.42	0.30
9	74	15.0	103	4.9	1.05	50.2	104.0	1.06	102.0	30.6	30.0	0.99	0.46	0.44	0.34
10	74	13.7	94	5.0	0.94	41.0	85.4	0.85	82.0	27.4	33.4	1.10	0.61	0.42	0.28
11	76	9.7	67	3.4	0.98	36.1	75.5	1.10	105.0	28.3	26.9	0.89	0.53	0.46	0.34
12	76	11.8	82	4.4	0.93	42.0	87.5	1.00	95.4	26.8	28.1	0.94	1.01	0.44	0.36
13	76	14.0	96	4.8	1.01	49.1	102.0	1.07	102.0	28.8	28.6	0.94	0.25	0.44	0.34
14	76	14.5	100	5.0	1.02	44.0	91.6	0.93	88.3	29.1	32.9	1.09	0.09	0.40	0.32
15	77	12.6	87	4.4	1.01	43.0	89.6	1.03	99.0	28.9	29.3	0.97	0.67	0.44	0.32
16	77	10.8	74	3.7	1.02	39.8	82.9	1.14	108.0	29.4	27.1	0.89	0.90	0.44	0.30
17	77	13.8	95	4.9	0.99	46.0	95.8	1.01	93.8	28.3	30.0	0.99	0.65	0.42	0.28
18	77	12.2	84	4.2	1.02	45.0	93.8	1.14	108.0	29.2	27.1	0.90	0.72	0.44	0.34
19	78	14.1	97	5.0	0.98	49.1	102.0	1.03	100.0	28.3	28.3	0.95	0.52	0.42	0.28
20	78	10.4	72	3.5	1.03	39.4	82.1	1.17	112.0	29.6	26.4	0.88	0.70	0.42	0.30
21	78	12.0	83	4.1	1.01	40.6	84.5	1.02	97.5	29.3	29.5	0.98	0.70	0.44	0.32
22	78	14.1	97	4.9	0.99	49.2	102.0	1.04	100.0	28.8	28.6	0.95	0.50	0.42	0.32
23	79	14.0	96	4.9	0.98	44.0	91.8	0.94	89.5	28.5	31.8	1.04	0.39	0.46	0.34
24	79	13.3	92	4.7	1.00	44.5	92.8	1.00	95.6	28.6	29.9	0.99	0.46	0.40	0.32
25	79	15.0	103	5.1	1.03	43.1	89.7	0.90	84.8	30.0	34.8	1.15	1.02	0.42	0.28
26	79	9.8	63	3.3	0.95	40.0	83.4	1.26	121.0	29.7	24.5	0.76	0.67	0.44	0.34
27	79	10.8	74	3.6	1.03	40.6	84.6	1.18	110.0	30.0	26.6	0.87	0.68	0.42	0.36
28	79	10.7	74	3.8	0.97	39.0	81.3	1.04	103.0	28.2	27.7	0.91	0.27	0.46	0.36
29	79	12.8	88	4.5	0.98	40.1	83.4	0.92	88.7	28.4	31.9	1.04	0.41	0.48	0.36
30	79	12.0	83	4.5	0.92	44.0	91.6	1.02	97.8	26.5	27.3	0.91	0.20	0.44	0.30
31	80	10.4	72	3.8	0.95	40.1	83.6	1.11	106.0	27.4	26.0	0.86	0.74	0.42	0.26
32	80	13.3	92	4.7	0.98	48.1	100.0	1.06	102.0	28.1	27.7	0.92	0.80	0.42	0.34
33	80	11.6	80	4.1	0.98	39.3	81.8	1.00	95.0	28.2	29.5	0.98	0.17	0.40	0.32
34	80	14.1	97	5.0	0.99	42.2	87.9	0.90	84.8	28.3	33.3	1.10	0.40	0.46	0.30
35	80	13.7	94	4.9	0.96	40.5	84.4	0.86	87.2	27.8	33.8	1.12	0.20	0.42	0.32
36	81	13.0	90	4.7	0.96	46.1	95.9	1.02	97.8	27.6	28.2	0.94	1.14	0.46	0.32
37	81	14.0	96	4.9	0.98	46.5	96.9	0.99	93.9	28.6	30.4	0.99	0.55	0.40	0.34
38	82	10.0	69	3.5	0.99	35.5	74.0	1.06	100.0	28.5	28.6	0.93	0.83	0.40	0.32
39	83	12.9	89	4.5	0.99	42.5	88.5	0.98	94.0	28.4	30.4	1.01	0.14	0.42	0.34
40	83	13.4	92	4.6	1.00	44.0	91.6	0.99	95.5	29.1	30.5	1.00	0.22	0.42	0.34
41	83	13.9	96	4.8	1.02	39.3	82.0	0.87	82.5	29.2	35.4	1.17	0.33	0.44	0.36
42	84	13.3	92	4.6	1.00	42.2	88.0	0.96	91.7	29.0	31.5	1.04	0.37	0.44	0.34
43	84	14.6	101	4.9	1.03	52.2	109.0	1.11	106.0	29.8	28.1	0.93	0.46	0.44	0.36
44	85	11.2	77	4.0	0.96	40.2	83.8	1.05	100.0	28.0	27.9	0.92	1.02	0.40	0.28
45	86	11.7	80	4.1	0.98	42.2	88.1	1.07	103.0	28.6	27.8	0.91	1.00	0.44	0.30
46	87	12.1	84	4.3	0.98	43.3	90.2	1.05	100.0	28.1	28.2	0.93	1.80	0.46	0.34
47	87	13.8	95	4.8	1.01	43.0	89.5	0.95	90.0	28.9	32.1	1.06	0.27	0.44	0.36
48	88	14.0	97	4.9	1.01	40.1	83.6	0.87	82.4	28.7	34.9	1.15	0.40	0.42	0.30
49	91	14.3	98	5.0	1.00	40.4	84.2	0.88	81.3	28.7	35.4	1.16	0.28	0.44	0.30
50	91	13.0	90	4.5	1.03	40.2	83.8	0.95	89.6	29.0	32.3	1.07	0.17	0.40	0.36
Av.	78.3	12.65	87.3	4.4	1.00	41.2	85.8	1.02	97.7	28.5	29.6	0.98	0.57	0.45	0.33

cell count of 4,500,000. The volume index is equal to the percentage of packed cells (see above), divided by the ratio of the red cell count to the "normal." The computed male values ranged from 0.85 to 1.26 with 1.02 as the mean value, and the female values from 0.66 to 1.20, with a mean value of 0.88.

Saturation Index. This is an indication of the amount of hemoglobin per unit volume of erythrocyte relative to the "normal." It is

TABLE 2.—EXPERIMENTAL AND CALCULATED VALUES FOR THE FEMALE GROUP

No.	Age	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb., $\gamma\gamma$	Mean. corp. Hb. con.	Saturation index	Reticulocytes, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
1	66	10.4	72	3.6	0.90	35	76	0.95	97	29.0	29.9	0.95	0.43	0.42	0.30
2	68	11.6	80	4.2	0.86	30	65	0.70	72	27.8	33.1	1.23	0.29	0.40	0.32
3	69	9.8	68	3.3	0.93	25	54	0.74	67.5	26.5	39.2	1.26	0.50	0.44	0.36
4	69	12.8	88	4.3	0.93	37	80	0.84	88	29.8	34.9	1.10	0.63	0.44	0.34
5	70	13.0	90	4.7	0.87	40	87	0.84	86	27.9	32.5	1.03	0.32	0.42	0.28
6	70	11.7	81	4.0	0.91	32	70	0.79	80	29.2	31.6	1.15	0.18	0.42	0.34
7	71	14.1	97	4.8	0.92	46	100	0.93	96	29.3	30.7	0.97	0.29	0.46	0.36
8	71	12.2	84	4.5	0.84	38	83	0.83	84	27.1	32.1	1.01	0.41	0.44	0.34
9	71	10.8	74	3.9	0.86	39	85	0.98	100	27.6	27.9	0.87	0.50	0.40	0.32
10	73	13.6	94	4.6	0.92	44	96	0.94	96	29.5	30.9	0.98	0.38	0.42	0.28
11	73	12.9	89	4.5	0.89	38	83	0.83	85	28.8	33.0	1.07	0.26	0.40	0.32
12	73	11.8	81	4.1	0.88	36	78	0.85	87	28.7	32.9	1.04	0.85	0.40	0.30
13	75	9.9	68	3.6	0.85	27	59	0.73	75	27.4	36.7	1.15	0.67	0.42	0.34
14	75	10.4	72	3.6	0.90	32	70	0.88	89	28.9	32.5	1.03	1.02	0.44	0.36
15	75	12.2	84	4.3	0.87	36	78	0.81	94	28.3	33.9	1.07	0.64	0.42	0.32
16	75	11.0	76	3.9	0.88	41	89	1.03	105	28.4	26.9	0.86	0.31	0.40	0.32
17	76	14.9	103	5.0	0.93	47	102	0.92	96	29.9	31.7	1.01	0.48	0.44	0.36
18	76	16.0	114	5.2	0.94	52	113	0.97	100	30.7	30.8	1.01	0.50	0.42	0.32
19	76	10.0	69	3.5	0.88	29	63	0.81	83	28.6	34.5	1.09	0.48	0.40	0.28
20	76	12.3	85	4.4	0.87	38	83	0.85	86	27.9	32.4	1.02	1.26	0.44	0.32
21	76	10.4	72	3.8	0.86	34	74	0.88	91	27.7	30.6	0.98	0.21	0.42	0.30
22	76	9.9	68	3.3	0.93	29	63	0.86	88	30.0	33.1	1.08	0.55	0.40	0.34
23	76	11.2	77	3.4	1.01	42	91	1.20	123	32.8	26.7	0.85	0.78	0.42	0.34
24	77	14.0	96	4.9	0.88	46	100	0.92	94	28.5	30.5	0.96	0.69	0.42	0.32
25	77	11.9	82	4.5	0.82	38	83	0.83	84	26.5	31.3	0.99	0.74	0.40	0.32
26	77	12.3	85	4.4	0.87	40	87	0.89	91	27.9	30.6	0.93	0.41	0.44	0.36
27	77	10.5	72	3.8	0.85	37	80	0.94	97	27.3	28.4	0.90	0.32	0.40	0.28
28	77	12.3	85	4.1	0.93	36	78	0.86	88	30.0	34.2	1.09	0.51	0.42	0.34
29	78	11.5	79	4.0	0.84	38	83	0.93	95	28.6	30.3	0.95	0.80	0.44	0.36
30	78	10.0	69	3.4	0.91	30	65	0.86	88	29.3	33.3	1.06	0.93	0.44	0.34
31	78	7.8	68	3.3	0.93	27	59	0.81	82	30.0	36.3	1.15	0.34	0.42	0.32
32	78	9.9	68	3.5	0.87	30	65	0.83	86	28.2	33.0	1.04	0.91	0.40	0.34
33	78	12.6	87	4.7	0.83	38	83	0.79	81	26.7	33.1	1.05	0.77	0.44	0.38
34	78	13.1	90	4.7	0.87	35	76	0.74	76	28.2	37.4	1.18	0.88	0.40	0.30
35	79	11.8	81	4.3	0.85	29	63	0.66	67.5	27.5	40.7	1.28	0.21	0.42	0.34
36	79	13.8	95	4.5	0.95	41	89	0.89	91	30.6	33.7	1.04	0.18	0.44	0.36
37	79	10.6	73	3.3	1.00	39	85	1.16	118	32.1	27.2	0.86	0.62	0.44	0.36
38	79	10.1	70	3.6	0.88	34	74	0.92	94	28.0	29.7	0.95	0.49	0.42	0.34
39	79	13.7	94	4.8	0.88	40	87	0.81	83	28.4	34.3	1.08	0.17	0.44	0.36
40	81	14.1	97	4.8	0.92	44	96	0.90	92	29.4	32.1	1.01	0.65	0.40	0.30
41	84	14.6	100	4.9	0.92	47	102	0.94	96	29.8	31.1	0.98	0.79	0.42	0.38
42	84	10.0	69	3.5	0.90	29	63	0.82	83	28.9	34.5	1.09	0.44	0.40	0.32
43	86	9.5	66	3.4	0.88	26	57	0.76	77	28.2	36.5	1.15	0.81	0.44	0.36
44	87	9.9	68	3.5	0.87	31	67	0.86	88.5	28.4	31.9	1.01	0.98	0.42	0.30
45	89	12.6	87	4.2	0.94	38	83	0.89	90	29.9	33.2	1.05	0.51	0.44	0.34
46	89	11.9	82	4.1	0.90	32	70	0.77	78	28.9	37.2	1.17	0.42	0.42	0.36
47	90	10.8	76	3.9	0.94	41	89	1.03	105	27.9	26.4	0.91	0.60	0.40	0.32
48	90	11.2	77	3.9	0.88	40	87	1.00	102	28.6	28.0	0.88	0.33	0.46	0.36
49	93	9.5	66	3.2	0.93	30	65	0.92	94	29.7	31.7	1.01	0.61	0.42	0.28
50	104	10.1	70	3.5	0.89	33	72	0.91	93	28.5	30.6	0.97	0.90	0.44	0.34
Av.	77.2	11.7	80.5	4.1	0.88	36.7	80	0.88	90.0	28.8	32.3	1.00	0.64	0.42	0.35

calculated by dividing the per cent hemoglobin by the percentage "normal" of the packed cells. The values varied from 0.76 to 1.17 for the males, and from 0.85 to 1.28 for the females. The average male saturation index was 0.98 and the average female saturation index was 1.0.

TABLE 3.—EXPERIMENTALLY DETERMINED AND COMPUTED VALUES FOR VARIOUS AGE GROUPS

Age group	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb., $\gamma\gamma$	Mean corp. Hb. con. %	Saturation index	Reticulocytes %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
							FEMALE							
65–69	11.2	77.4	3.9	0.90	32	70	0.81	81.1	28.3	34.4	1.13	0.46	0.42	0.33
70–74	12.6	87	4.5	0.89	40	86	0.88	89.6	28.5	31.2	1.01	0.33	0.42	0.32
75–79	11.7	81	4.1	0.89	36	79	0.96	90.0	28.9	32.4	1.02	0.59	0.42	0.33
80–84	12.9	89	4.4	0.92	40	87	0.88	90.6	29.4	32.6	1.02	0.63	0.41	0.30
85–89	11.0	76	3.8	0.90	32	69	0.82	81.1	28.8	34.7	1.09	0.68	0.43	0.34
90–94	10.5	72	3.7	0.91	37	81	0.98	100.0	28.7	28.7	0.93	0.51	0.42	0.32
95+	10.1	70	3.6	0.89	33	72	0.91	93.0	28.5	30.6	0.97	0.90	0.44	0.34
							MALE							
65–69	12.8	88	4.5	1.00	45.5	95	1.03	102.0	28.5	28.2	0.93	0.48	0.43	0.32
70–74	12.9	89	4.5	0.98	42.3	88	0.98	95.7	28.3	30.2	1.00	0.62	0.43	0.31
75–79	12.4	86	4.3	0.99	42.9	89	1.09	101.0	28.7	28.9	0.95	0.57	0.43	0.32
80–84	12.9	89	4.5	0.99	43.0	90	0.99	93.0	28.5	30.3	1.00	0.49	0.43	0.33
85–89	12.5	96	4.5	0.99	41.7	87	1.01	95.1	28.5	30.1	0.99	0.90	0.44	0.32
90–95	13.6	94	4.7	1.01	40.3	84	0.91	85.5	28.9	33.8	1.12	0.22	0.42	0.33

These indices are to be found in Tables 1 and 2, with the mean values for the different age groups of both sexes in Table 3.

Mean Corpuscular Volume. This figure represents the volume of the average erythrocyte in cubic micra, and is computed by dividing the absolute volume of packed cells per 1000 cc. of blood, by the red cell count in millions per c.mm. The mean corpuscular volume in the male subjects ranged from 81.3 cu. micra to 121 cu. micra, with a mean value of 97.7 cu. micra, and that for the females from 67.5 to 123 cu. micra, the mean value being 90 cu. micra.

Mean Corpuscular Hemoglobin. This is the average weight of hemoglobin in each red cell, expressed in micromicrograms. (A $\gamma\gamma$ is equal to 1×10^{-12} gm.) It is equal to the grams of hemoglobin per 1000 cc. of blood divided by the red cell count in millions per c.mm. Our male subjects showed a mean corpuscular weight between 26.5 and 30.6 micromicrograms, while the mean weight for the females was from 26.5 to 32.1 micromicrograms. The average values fell at 28.5 micromicrograms for the males and 28.8 micromicrograms for the females.

Mean Corpuscular Hemoglobin Concentration. This value is a measure of the average concentration of the hemoglobin in the erythrocyte, expressed as a percentage. It is computed by dividing the grams of hemoglobin per 100 cc. of blood by the volume of packed cells in cc. per 100 cc., and multiplying the resulting decimal by 100. The range of values for the male group was between 24.5 and 35.4%, the average

being 29.6% and for the females, between 26.4% and 40.7%, with an average of 32.3%.

All of the above mentioned values may be found in Tables 1 and 2, with the average for each age group in Table 3.

Discussion. These experimentally determined and computed values, to the best of our knowledge, comprise the first study in a group of this type using the computation of all the hematologic constants.

The findings presented in this paper may be compared with values appearing in the literature for comparable groups, by referring to Table 4. In Table 4, we have outlined the results of investigations by several observers into the hemoglobin, erythrocyte counts, and hematocrit readings of normal individuals past 60 years of age.

TABLE 4.—COMPARISON OF RESULTS OBTAINED BY DIFFERENT INVESTIGATORS

Authors	Ref. No.	Age group	Sex	Hb.	RBC	Packed cells	Remarks
Leichenstern	8	60 and up	M	14.3			Cited by Kilduffe
			F	13.1			
Williamson	28	61–70	M	16.3	..	..	Spectrographic method
		71–75	M	15.5			
		61–70	F	15.8			
		71–75	F	15.3			
Cameron and Nicholson	2	66–70	M	16.1			
		71–75	M	15.2			
		75–	M	15.7			
		66–70	F	15.6			
		71–75	F	15.4			
		75–	F	15.1			
Nelson and Stoker	13	60 and up	M	15.5	5.22		
Miller	12	60 and up	M	14.3	4.46		
Fowler *et al.*	4	60 and up	M	13.1	4.61	41.4	Also found that the presence or absence of free HCl in the stomach had no bearing on the blood findings
			F	11.9	4.47	40.0	
Newman and Gitlow	..	65 and up	M	12.7	4.42	41.2	
			F	11.7	4.10	36.7	

In reviewing the early literature, we were struck by the fact that no differentiation was made between the sexes when hematologic studies were done on individuals past 60 years of age. Whether this is due to the small number of cases reported upon, and hence the necessity for grouping the males and the females for a statistically reliable number of cases, we do not know. It is known that young healthy females have normal values for hemoglobin, erythrocytes, and hematocrit readings that are lower than the corresponding values for males. Several theories have been advanced to account for this.[3,9,15] But when we study the results of investigations into the hematologic sex differences in the aged, none of these theories seem to explain these differences satisfactorily. The theory of the loss of iron during menstruation does not explain the lower hemoglobin of a group of 80-year old women than that shown by a group of 80-year old men. The explanation that younger women lead a less active life than the men and hence need less hemoglobin to transport the oxygen necessary for their metabolic processes may possibly be true; but both aged men and aged women lead sedentary lives. Probably for females below the age of menopause, both these factors are involved. In any case,

these sex differences that are found in the aged may be a carry-over from younger days. That such a difference does in fact exist in the aged, may be seen from an inspection of Table 5, wherein we have presented the average findings of this study for both sexes together with the standard deviations and probable errors, in order to show that the ratio of the difference between the means to the square root of the sum of the squares of the probable errors is considerably greater than 6, which is the criterion for statistical significance.

TABLE 5.—COMPARISON OF RESULTS FOR MALES AND FEMALES

	Hb., gm. per 100 cc.	Hb., %	R.B.C., mill. per c.mm.	Color index	Packed cells	% packing	Volume index	Mean corp. vol., μ^3	Mean corp. Hb., $\gamma\gamma$	Mean corp. Hb. con. %	Saturation index	Reticulocyte count, %	Hemolysis starts, % salt solution	Hemolysis complete, % salt solution
M♂	12.7	87.5	4.42	0.99	41.2	85.8	1.02	97.7	28.5	29.6	0.98	0.53	0.45	0.33
S.D.♂	1.48		0.158		4.27		0.086	8.5	0.85	2.61				
P.E.♂	0.0199		0.0021		0.0576		0.0012	0.115	0.0115	0.0352				
M♀	11.7	80.5	4.10	0.88	36.7	80.0	0.88	90.0	28.8	32.3	1.0	0.64	0.42	0.35
S.D.♀	1.62		0.176		6.05		0.101	20.9	1.28	3.06				
P.E.♀	0.0218		0.0024		0.081		0.014	0.283	0.0173	0.0413				
$\frac{M♂ - M♀}{\sqrt{P.E.^2♂ + P.E.^2♀}}$	33		98		46		80	27	15	50				

M♂ = Average male value
S.D.♂ = Standard deviation for males
P.E.♂ = Probable error for males
M♀ = Average female value
S.D.♀ = Standard deviation for females
P.E.♀ = Probable error for females.

The expression $\left(\frac{M♂ - M♀}{\sqrt{P.E.^2♂ + P.E.^2♀}}\right)$ is the criterion for statistical significance. It should be greater than 6

Perusal of Table 4 brings out several interesting facts. First, as the reports approach the present, the mean values for the various studies seem to become lower. This may be due to an improvement in method, or with the increase in food processing that has taken place of recent years, the iron intake may be actually lower than it has been. Second, the results of studies made by Fowler *et al.*,[4] Miller,[12] and by us, seem to indicate that the physiologic "normals" for the aged, as reported in several textbooks as well as in the literature are too high. Hence, in reporting the hemoglobin, in view of the controversy over what is "normal" for the aged, results should be stated in terms of grams per 100 cc., and when the various hematologic constants are calculated, the "hemoglobin coefficient" be used as 100%. The "hemoglobin coefficient" is the grams of hemoglobin per 100 cc. of blood calculated to an erythrocyte count of 5,000,000 in the case of males, and to a count of 4,500,000 in the case of females.

The number of red cells in the blood of healthy males is usually thought to average in the neighborhood of 5,000,000 cells per c.mm. The average number of red cells for young healthy females is around

4,500,000 cells per c.mm. Our data for both males and females fall below these values. The work of Fowler *et al.*[4] likewise points to a lower average value. It should be noted that in spite of the slight difference between the mean value of the erythrocyte count in the male and that in the female, Table 5 shows that the difference is real and statistically significant.

A great difference may be seen to exist between the male and female "normal" hematocrit values and the corresponding mean values determined by us. Similarly, Fowler *et al.*[4] working with 100 males past the age of 60 years, found that the hematocrit readings averaged 41.4 cc. of blood. Hence, it is the opinion of the authors that instead of 48 or 46 cc.[29] being used as the "normal" hematocrit reading for aged males or females, the value, 42 cc. would seem to represent a truer normal male value, while for the females, a still lower average normal, about 38 cc. be used. (Osgood and Wilhelm[16] report a mean packed cell volume of 42 cc. for young healthy males.)

The mean corpuscular volume as determined for young healthy individuals and reported by Wintrobe[29] is 87 cu. micra. The mean value found by us for the male subjects namely, 97.7 cu. micra, as well as the mean values for the females, 90 cu. micra, are both larger than this value. Table 5 shows the difference between the male and female mean values to be truly significant.

Wintrobe[29] likewise reported that the mean corpuscular hemoglobin was from 27 to 32 micromicrograms. Our mean values for either sex fall within these limits. Despite the small difference between the means (28.5 $\gamma\gamma$ for the males, and 28.8 $\gamma\gamma$ for the females), the difference is truly significant (Table 5).

The normal variation for the mean corpuscular hemoglobin concentration has been reported as from 32% to 38%.[29] Our mean male value of 29.6% is lower than this, while the mean female value of 32.3% falls just within these limits.

Haden[6] has shown that the diminished resistance of erythrocytes to hypotonic salt solutions is probably not due to any abnormality in the chemical make-up of the cell, but rather to changes in its shape. When the red cells are immersed in a hypotonic salt solution, they change from a flat biconcave disk to a sphere before rupture occurs. The more nearly spherical they are to begin with (as in the case of hemolytic jaundice, where spherocytosis is pronounced), the less they can swell before rupture of the cell membrane takes place. Our subjects showed normal resistance to hypotonic saline solutions. It may therefore be reasoned that the shape of their cells is similar to the shape of the cells in younger healthy individuals. Furthermore, the normal values reported elsewhere for fragility studies may be applied with safety when dealing with the blood of individuals past 65 years of age.

Various observers present values for the reticulocyte percentage in normal individuals ranging all the way from less than 0.1% up to more than 2%.[1,8a,10,22,27] Our data fall in between these two values. We could find no correlation between the percentage of reticulocytes and any other determined or computed value. This was to be expected,

since the formation of new erythrocytes is independent of the circulating cells.

No significance could be attached to the difference between the sexes as far as the values for the saturation index, the reticulocyte count, or the resistance of the erythrocytes to hypotonic saline.

It should be stated at this point, that several of the experimental group presented findings that at first glance are open to diagnostic question. For example, Male Subject 11 showed a volume index of 1.10, using the usually accepted normal values, and a slightly elevated mean corpuscular volume. This is suggestive of a pernicious anemia. However, since the subject showed no other signs or symptoms, and in view of the color index, which was below 1, the individual was treated as a normal. Similarly for Male Subject 31. Low values for the various indices, as for example Male Subject 10 with a volume index of 0.85, No. 35 with a volume index of 0.86, and No. 41 with a volume index of 0.87, were treated as low normals, in view of the normality of the other findings, rather than secondary anemias.

In a subsequent paper, we shall present our findings dealing with a study of the leukocytes of the normal aged individual.

Conclusions. 1. Determinations were made of the hemoglobin, the erythrocyte count, the volume of packed cells, the reticulocyte count, and the resistance of the red cells to hypotonic salt solutions in a group of 100 individuals past 65 years of age.

2. The color index, volume index, saturation index, the mean corpuscular volume, the mean corpuscular hemoglobin, and the mean corpuscular hemoglobin concentration were computed.

3. Comparisons were made with "normal" values reported by other observers.

4. It was found that the physiologic "normals" should be modified when dealing with aged individuals.

5. There is a statistically significant difference between the male and female values as determined by us for hemoglobin, red cell count, hematocrit readings, volume index, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

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A STUDY ON THE VALUE OF A MIXED BACTERIAL "ORAL COLD VACCINE"

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As is true of a number of virus diseases, the common cold acquires clinical and pathologic significance because of the secondary complications arising from superimposed bacterial pathogens. Since prophylactic immunization directed in this case towards the virus itself is not at present attainable, attempts have been made to solve the problem by reducing the number or severity of the secondary complications by artificially increasing resistance to the potentially virulent bacteria of the upper respiratory tract. Vaccines of mixed bacteria administered by one route or another have been given experimental trials, but as yet the results reported have been of varying success.[1–15] The desire to protect its personnel against recurring colds induced the Visiting Nurse Service of New York City to undertake a study of its own on the effectiveness of bacterial vaccines in preventing the more usual respiratory complications. The conditions seemed to be par-

ticularly favorable for a satisfactory test since daily reports could be made available on a group of coöperative individuals whose work exposed them frequently and intimately to acute respiratory infections.

Plan of Study. The Henry Street Visiting Nurse Service provides home nursing care for the sick. About 500,000 visits to approximately 100,000 cases are made each year. The personnel consists of about 300 nurses and 70* office workers distributed among 15 centers in Manhattan, The Bronx, and Queens, and an administration office in Manhattan.

The study was limited to volunteers of the nursing and office staffs. About 70% of the personnel volunteered. They were divided into 2 groups depending upon the number of colds experienced in the preceding year. Each group was further subdivided into those with (*a*) chronic sinusitis, bronchitis, or otitis, (*b*) allergies and (*c*) no clinical manifestations—making 6 classifications in all. The names of those in each classification were sorted according to branch office. Within each office, the individuals studied were arranged alphabetically by name and allocated alternately to control and test groups without their knowledge.

For purposes of immunization a commercial product composed of mixed, heat-killed bacteria (*i. e.*, about 25 billion pneumococci, 15 billion streptococci, 5 billion *H. influenzæ*, and 5 billion *M. catarrhalis* per dose) was prepared in the form of capsules to be taken orally. The control group, on the other hand, was given capsules identical in appearance and containing the same ingredients *without* bacteria.† Both types of capsules were distributed in the same kind of container labeled with identical directions for use and containing enough capsules for the entire test period. Single capsules were taken daily for the first 14 days, and twice weekly thereafter, as recommended by the producer and distributor of the product.

Each day a report was made of the number of capsules taken, of any symptoms of infection of the respiratory tract, and of any days off duty because of respiratory illness. The data were contained in the regular report of activities which are recorded daily by the personnel. Punch cards and machine tabulators were used to collect and analyze the data.

The test period lasted from September 3, 1940 through March 30, 1941, a period of 210 days. It began 14 days after the first capsule was taken on August 19, and ended on March 30 for those completing the study, or before March 30 for those who dropped out. A summary of the number of individuals in each group and of the number of person-periods of observation follows:

TABLE 1

	Group		
	Test	Control	Total
Number of persons in study:			
Total	125	128	253
Duration of observation:			
Entire period (210 days)	71	76	147
Part of period (less than 210 days)	54	52	106
Number of person-periods‡ of observation	112	111	223

The groups were almost equal in size and in duration of follow-up. They were comparable in regard to the number and duration of respiratory infections in the preceding year, and in the number of days off duty on account of such illnesses. About 95% of the individuals were from 25 to 40 years of age.

* This number includes members of departments serving both the Visiting Nurse Service and the Henry Street Settlement.

† We wish to thank Eli Lilly & Co. for supplying both forms of capsules used in the study.

‡ On the basis of 210 days per person.

Results. Each group had 239 colds during the test period in 1940–41. A summary of the number of colds in 1940–41 among those with "few" (less than 3) or "many" (3 or more) colds during the same period of the preceding year follows:

TABLE 2

No. of colds during test period (1940–41)	Total		Those with less than 3 colds in year preceding test period		Those with 3 or more colds in year preceding test period	
	Test group	Control group	Test group	Control group	Test group	Control group
0	20	16	9	9	11	7
1	29	40	14	19	15	21
2	42	40	14	20	28	20
3	17	16	8	4	9	12
4	10	10	5	2	5	8
5	7	5	3	1	4	4
6	0	1	0	0	0	1
Total (persons)	125	128	53	55	72	73
Person-periods of observation	112	111	50	49	62	62
Colds	239	239	101	84	138	155
Colds per person-period	2 1	2 2	2 0	1 7	2 2	2 5

Among those with 3 or more colds in the preceding year, fewer colds were reported during the test period by 54 (75%) of the inoculated and 48 (66%) of the controls. Among those with less than 3 colds the year before, more colds were reported during the period of observation by 16 (30%) of the inoculated and 7 (13%) of the controls. The number of colds per person-period of observation during the test period was 2.1 for those receiving the vaccine and 2.2 for those taking the control capsules. It was slightly higher for the inoculated than the controls among those with less than 3 colds in the preceding year, and slightly lower for the inoculated than the controls among those with 3 or more colds in the preceding year.

The average duration of symptoms experienced by the group taking the vaccine was 10.5 days per cold, as compared with 9.7 days for the control group. On the whole, the duration of symptoms was longer than that reported in most other studies, partly because symptoms were recorded daily and partly because symptoms recurring within a period of less than 7 days were not attributed to a new cold but to the old one.

The number of days of absence during the test period on account of respiratory illnesses varied from 0 to 43. The distribution of the inoculated and controls according to the number of days of absence is shown in Table 3.

About 33% of the persons in each group had no absences. An additional 25% to 30% were absent from 1 to 2 days, and about 15% to 20% from 3 to 4 days. In all, 80% of the inoculated and 76% of the controls had from 0 to 4 absent days during the 7-month period of observation. About 13% in each group were absent from 5 to 7 days, and 8% from 8 to 21 days. The distribution of inoculated and control persons according to the number of days absent was, therefore, fairly parallel over the range from 0 to 21 days which included all of the

inoculated and 98% of the controls. Three controls, comprising 2% of the group, were absent 25, 40, and 43 days, respectively, a total of 108 days. They increased by 30% the number of absent days in the control group, and raised the arithmetic average for the group to 4.2 days per person-period of observation as compared with 3.1 for the inoculated. On the other hand, the median values for the groups were 2.0 and 2.2 absent days respectively, for inoculated and control individuals.

TABLE 3

No. of days absent during test period	Test group		Control group	
	No.	% distribution	No.	% distribution
0	42	33.6	42	32.8
1–2	40	32.0	31	24.2
3–4	18	14.4	24	18.8
5–7	15	12.0	17	13.3
8–14	7	5.6	8	6.3
15–21	3	2.4	3	2.3
22–43	0	0.0	3	2.3
Total (persons)	125	100.0	128	100.0
Person-periods of observation	112	..	111	
Days absent:				
(*a*) Total	342	..	462	
(*b*) Average	3.1	..	4.2	
(*c*) Median	2.0	..	2.2	

About 40% of the illnesses in each group appeared to be uncomplicated head colds and about 60% were somewhat more severe or associated with complications. A summary of the latter cases in each group follows:

TABLE 4

Nature of illness	Total	Test group	Control group
Bronchitis	86	41	45
Grippe or influenza	55	26	29
Otitis	11	7	4
Pneumonia	3	2	1
Tonsillitis	110	56	54
Total cases	265	132	133

The cases which had complications or were considered more severe than a head cold were fairly evenly distributed between the two groups.

During the period of observation, a few persons in the control and inoculated groups volunteered the opinion that they were being helped by the capsules taken. Unfortunately, a survey on this point was not made at the end of the study before the names in each group had been announced.

Comment. The evidence outlined in this report indicates that the oral administration of a commercially prepared vaccine of mixed killed bacteria as described above failed: (1) to decrease the incidence of acute respiratory infections, (2) to reduce the severity or duration of such infections, and (3) to prevent secondary bacterial complications. A group of individuals observed for purposes of control ran remarkably similarly to those receiving vaccines. Thus, both control and inoculated groups had exactly the same number of colds, and there

was no significant difference between the groups in the duration of symptoms and in the number and variety of complications following the colds. These observations strengthen those already made by various investigators[1,4,5,11] that contrary to fairly widespread medical and lay opinion so-called "cold vaccines" are of questionable value as a prophylactic measure both against the common cold and its bacterial complications.

Since the method of immunization was *per os*, it may be that antibody formation may not have been adequate; or it may be as Walsh[13,14] postulates, that the immunity stimulated in such cases must be local (*i. e.*, stimulated by application of the vaccine topically to the membranes of the upper air passages). However, the latter assumption is based on inconclusive data, and if true then it must be assumed that immunity to bacteria of the respiratory tract belongs to a special category, since general methods of administration of vaccines such as subcutaneous, intramuscular, intraperitoneal, and intravenous have been successful in inducing prophylactic immunization in a variety of infections.

On reflection, it is difficult to see why a bacterial vaccine composed of a few arbitrarily selected organisms, administered by any route, can be effective against the greater bulk to which the respiratory tract is exposed. The specific effects of such vaccines are limited to the relatively few bacterial types of the species employed since no consideration is made of the multiplicity of types of streptococci, pneumococci, and other pathogenic microörganisms. Furthermore, the nonspecific effects of the vaccine are of questionable value and, therefore, not dependable. However, in the face of continued recommendations based on personal experiences from both physicians[2,8,9,10] and lay people, it became necessary to derive definite information from a controlled study. As reported above, this has ended with the contrariwise opinion of the ineffectiveness of "oral cold vaccines."

Conclusions. The oral administration of a heat-killed vaccine containing several species of potentially pathogenic bacteria of the upper respiratory tract appeared to have no influence either on the incidence or severity of the common cold. Similarly, no effect was observed as a result of this treatment on the secondary complications frequently associated with the common cold. A group of control individuals receiving similar preparations without bacteria paralleled closely in almost every way the infections observed in the individuals receiving the vaccine.

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HEMOTHORAX IN BLOOD DYSCRASIAS

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Though the blood dyscrasias associated with abnormal tendency toward bleeding, such as the purpuras, scurvy, and hemophilia are usually mentioned as possible causes of non-traumatic hemothorax, actual case references in the literature are rare.

Prior to 1900, there were two such references: Kempf,[2] who described hemothorax complicating a case of scurvy; Pitt,[3,4] who, in reviewing 65 cases of hemothorax, mentioned 1 associated with purpura.

Since 1900 there appear to have been no such cases described.[1] Consequently, it was deemed advisable to report 2 cases of hemothorax which were admitted to the Jewish Hospital in a period of 2 months. Both occurred in males, 1 due to hemophilia, and 1 to thrombocytopenic purpura.

It is to be noted, of course, that a distinction is to be made between true blood in the pleural cavity and a pleural effusion, which is blood stained or hemorrhagic. The latter is not uncommon and is frequently seen accompanying malignant and lymphoblastomatous disease of the intrathoracic structures. The former, however, in the pure form, on a non-traumatic basis, is uncommon.

Case Studies. Case 1. L. S., a 22 year old white male was admitted to the Jewish Hospital in February 5, 1936, complaining of intense anterior left chest pain of about 36 hours duration. The pain was spontaneous in onset, accentuated by motion and respiration, associated with marked pallor, and followed by the passage of two tar-colored stools. Past history revealed that in 1928, at the age of 14, he bled continuously for about 4 weeks after a tonsillectomy. In 1933, following a tooth extraction he again bled profusely, and at the time it was discovered that he was a hemophiliac. Family history indicated that there was a strong background of hemophilia on the maternal side, the paternal relatives were free of the disease (Fig. 1).

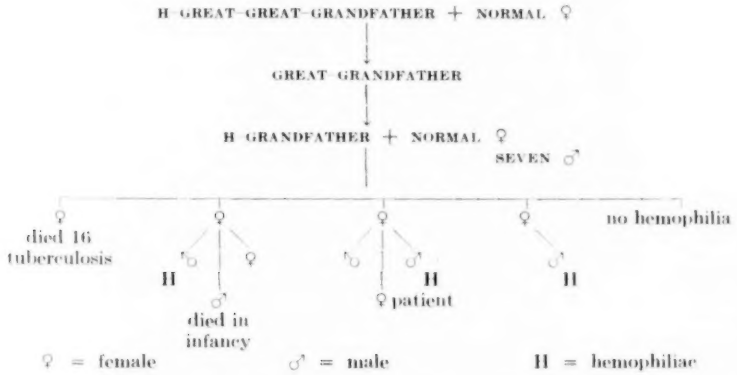
On admission he appeared exsanguinated, slightly cyanotic, and restless. The pulse rate was 80, respiratory rate 26, temperature was 97°, and the blood pressure was 80/20. There were signs of fluid in the left chest. Right chest was clear, and heart was displaced to the right. He was transfused several times. Two days after admission, 450 cc. of blood, fluid in character, was

obtained from the left pleural cavity. The next day 500 cc. was removed and a day later 400 cc. was removed. During this period, he received numerous small transfusions. Following this, the patient gradually improved, his respiratory distress disappeared and his bleeding ceased. He was discharged about 30 days after admission, much improved.

	Bleeding time	Clotting time
Feb. 6	5½ min.	3¾ min.
Feb. 7	4½ min.	3¼ min.
Feb. 19	4½ min.	5 min.

Other laboratory data were non-contributory.
N.B.—Unusual values in hemophilia.

FIG. 1.—Family tree of Case 1



Roentgen Examination of Chest (Fig. 2) (February 6). There is a homogeneous density extending from left apex to base. The diaphragmatic shadow is obliterated. The heart and trachea are displaced to the right. The rib shadows are not obscured.

Conclusions. Complete left hemothoracic effusion, probably blood.

February 28: Considerable absorption of pleural effusion. Heart and trachea now in normal position. Density along left upper lateral chest wall probably due to residual encysted effusion (Fig. 3).

CASE 2. A. G., a 26 year old white male was admitted to the Jewish Hospital on April 3, complaining of epistaxis of 2 days duration, spontaneous in onset. He had had similar but milder episodes in the previous 12 years, and had always demonstrated a bleeding tendency. There was no relevant familial history, nor any history of drug intake. On physical examination numerous ecchymotic areas of various ages were present over both arms and legs, and bleeding from the nose had ceased. Heart and lungs were natural. Liver was felt 3 cm. below costal margin, the spleen was just barely palpable and was tender in percussion. Except for a moderate hypochromic anemia, a leukopenia, laboratory studies revealed a thrombopenia. On successive days, platelet count was 2200, 2300, 2750 and 2500/mm3. Coagulation time was 3½ minutes, ½ hour +. He was given daily intramuscular injections of thromboblast, in daily intravenous doses of calcium gluconate and repeated blood transfusions.* One dose of Roentgen ray over splenic area was given (186 Kvp, 30 ma., ½ Cu 2 Al, 50 cm., 80 R″). He was discharged improved on April 26, 1936, with a platelet count of 11,000.

He was readmitted on May 6, suffering from blood loss. During the interval he had received splenic irradiation. However, on May 3, he began to have

* Some of this and subsequent therapy has been subsequently shown to be empiric.

tarry stools, and subsequently became progressively weaker. On admission, he gave evidence of chronic exsanguination, râles and dullness were present at

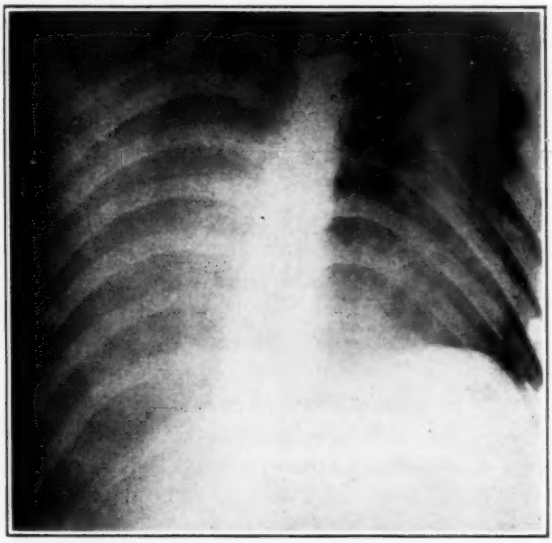


FIG. 2.—Note the massive left pleural hemothorax producing marked cardiac and mediastinal displacement to the right.

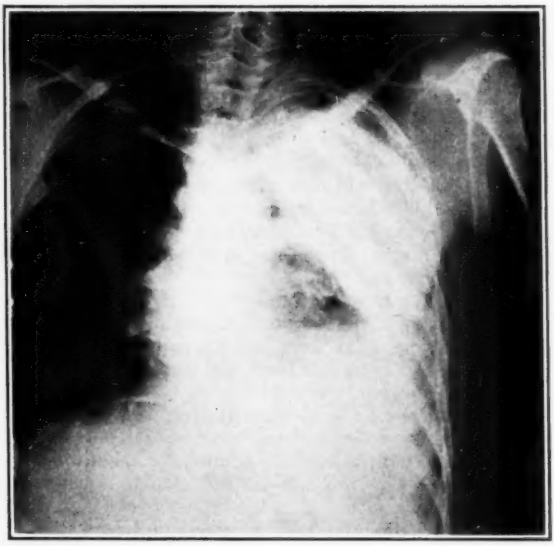


FIG. 3.—There is partial absorption of the hemothorax which is now loculated.

both pulmonic bases, the abdomen was slightly distended and the spleen barely palpable. Again there was a marked hypochromic anemia (Hgb., 4.3 gm.) and leukopenia (white blood count was 950); platelet count was 5250.

Treatment was similar to that on the previous admission including thromboblastin, direct blood transfusions, cevitamic acid, moccasin snake venom as well as liver extract.

On May 11, 5 days after admission, there were clinical evidences of fluid in the left chest. On May 18, there was evidence of displacement of the mediastinum to the right and respiratory embarrassment appeared. On that date, by thoracentesis 450 cc. of bloody fluid was obtained, and on May 21, 150 cc. of similar fluid was removed. Shortly afterward patient's temperature began to fluctuate in a septic fashion. Apparently unrelated to transfusions he began to have chills, abdomen became distended and blood was noted in the stools. On May 25, incision and drainage of left chest yielded greenish yellow pus. Culture subsequently revealed presence of *S. aureus*, and patient was given bacteriophage in addition to other measures. However, his septic course continued, though blood cultures were always negative, and on June 10 he died. Postmortem revealed intestinal mucous membrane hemorrhages, perforated left diaphragm, left sanguinopurulent empyema, necrosis of left lower lobe of lung. No bone marrow studies were done.

FIG. 4.—Massive left pleural effusion with considerable cardiac displacement to the right.

Roentgen Examination of Chest (Fig. 4). Almost complete uniform density from apex to base of left hemothorax. Heart is displaced to the right.

Conclusions. Pleural effusion, probably blood.

Discussion. Two cases of hemothorax occurring in males of the third decade with an abnormal bleeding tendency are presented. In neither was it a primary manifestation of the disease. In the hemophiliac it was acute in clinical onset, while in the purpuric it was more insidious. As is indicated by the course in the former it is not necessarily fatal. The extreme danger of infection which may be introduced from without is emphasized by the outcome in the latter. Therapy, as in all cases of hemothorax is somewhat controversial. Certainly if the onset is with shock, that should be treated first. As the bleeding

undoubtedly is diffuse and not focal in origin there is probably never an indication for thoracotomy and vessel ligation.

Aspiration is usually indicated after about 48 hours, as blood left in the pleural cavity may form fibrin clots, the latter requiring thoracotomy. The entire collection should be removed in one or two aspirations as the fewer the punctures the less danger there is of infection.

Replacement pneumothorax is probably of some value in certain cases to prevent a sudden change in intrapleural pressure. It is questionable if it is of any value in controlling bleeding, while it probably does increase the tendency toward pleural adhesions and its serious consequences.

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TREATMENT OF THE HYPERTENSIVE PATIENT IN THE PRE-CARDIAC STAGE

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At the present time there is only one treatment in the pre-cardiac stage of essential hypertension, and that is a rational medical management. How such treatment is effected and what constitutes a sensible management is an extremely debatable topic. One has only to review the literature on hypertension in the past two decades to find the truth of this statement.

My own views, tempered by the intensive experience of 10 years, are strongly conservative. Careful consideration needs to be given the hypertensive patient and his symptoms; he may require treatment for his "way of life" and for the alleviation of complications, such as obesity, nervousness and so on, rather than to reduce elevated blood pressure. I feel that nothing should be used when it makes the hypertensive patient more uncomfortable, such as the restriction of proteins or salt in his diet; that any drugs used should not have toxic manifestations, such as the sulfocyanates may produce; and that nothing should be employed which is time-consuming or expensive, such as so-called specific surgery. The hypertensive patient will sacrifice a great deal to obtain the therapy while imbued with hope for permanent relief, which does not exist at the present time. Essential hypertension is not an entirely hopeless disease, and the hypertensive patient should not and need not be unjustly inflicted with a constant fear for his life.

Principles of Treatment. Experienced practitioners have long recognized that drugs can reduce blood pressure, but only for short periods (Bishop[9]); that patients with high blood pressure might get better or worse according to what they were told of the figures, and that too

frequent blood pressure estimations might depress the patient (Potter[36]); and that headaches and dizziness, supposed to be due to high blood pressure, may disappear with laxatives and diet and no change in blood pressure (Nicholson[31]).

From such writings the few well-established principles in the treatment of the hypertensive patient have developed: (1) the effects of drugs on the elevated blood pressure are transitory; (2) attention should be focused away from the blood pressure; and (3) the symptoms may be relieved by simple means without any change in the blood pressure.

A rational management may accomplish a great deal. In a small number of hypertensive patients the blood pressure may return to normal, and the symptoms disappear, permanently or for a prolonged period of time. Such remissions often recur spontaneously when the individual leads a well regulated life. In a somewhat larger number there is subjective improvement with some lowering of the blood pressure, although not to a normal level. In the largest group of hypertensive patients the blood pressure is not lowered much, if at all, but the symptoms are relieved and the patients are comfortable.[43a]

Protein, Salt, and Fluid Consumption. Hypertensive patients are still seen who have been advised at one time or another not to eat red meat, or to use salt on their food, and to limit markedly the amount of fluids consumed daily. A few patients enjoy such a régime, for a while, as it gives them something that is different and temporarily adds interest to their presence among friends. The majority tires of the restrictions but are afraid to alter their diet unless assurance is given that such substances as red meat, salt, and fluids, in ordinary dietary amounts, have no effect on the labile blood pressure. One may safely give such assent to the hypertensive patient in the precardiac stage, for it is definite that no relation exists between the use of protein,[2] salt,[2,7,18,24,29,32] normal fluid intake,[2] and the elevation of the blood pressure. Robert,[37] who advocated the salt-free diet, cautioned that a rigid diet of this type, if protracted too long, may cause uremia.

Medicinals. A simple list of all the drugs employed in the treatment of essential hypertension is not only lengthy but confusing. A valuable contribution, which clarified the problem, was made by Ayman.[3a] He showed that the symptoms associated with uncomplicated essential hypertension may be frequently relieved by the suggestion inherent in any seriously and enthusiastically prescribed drug or method of therapy.

Sulfocyanates. Sulfocyanates (thiocyanate) are probably the most widely advocated drugs for the treatment of hypertension. They[19,30] were found to reduce the elevated blood pressure, and for a few years were used extensively. When untoward symptoms,[3b,34] such as marked weakness and angina pectoris, distressing side reactions, toxic manifestations, and death, occurred from its incautious use, the drug was dropped by many.[4,15,23] Nobody should use it except in carefully selected occasional cases, and with the proper care to avoid harmful reactions. Sedatives, such as phenobarbital, relieve the symptoms

better than the sulfocyanates;[17] but the latter causes a drop in blood pressure which is neither permanent nor necessarily desirable.

When Barker[5a] introduced the method of controlling the dosage by the blood concentration, the use of the drug was revived. Barker and his co-workers[42] have done good service by emphasizing the toxicity of the thiocyanates. They hope that their method of blood cyanate determinations will serve as a warning of the dangerous possibilities as well as a useful guide. Without such determinations they feel that the drug should not be used.

However, Garvin[21] presented a case with fatal toxic manifestations which is significant in that the untoward symptoms occurred while the blood cyanates were at a supposedly non-toxic level. Russell and Stahl[39] reported a case in a hypertensive patient who had received only a total of 5.6 gm. of potassium thiocyanate over a period of 14 days. Robinson and O'Hare[38] treated 75 ambulatory hypertensives with potassium sulfocyanate and followed them closely by blood cyanate studies; toxic symptoms occurred in 29 (38%). In 23 of the 29 these consisted of nausea, weakness, dermatitis, purpura, and a decrease in libido. Serious complications consisting of dermatitis exfoliativa, congestive heart failure, cerebral thrombosis, angina pectoris, and psychoses occurred in 6 cases. In spite of such a large number of toxic manifestations, they concluded that this form of treatment in uncomplicated vascular hypertension in patients under 60 years of age, when carefully controlled, has decided value. Satisfactory results have been reported by Barker and his co-workers,[5b] Blaney and his collaborators,[10] Cannady and Allen,[12] Caviness and his associates,[13] and Kurtz *et al.*[26]

I myself have not used thiocyanate therapy to date in any hypertensive patient. My reasons are simple. When I began work in the out-patient dispensary of the Mt. Sinai Hospital, my colleague in the next room (Dr. Henry Siegel), who had preceded me there by 2 years, was employing the thiocyanates for such patients. Therefore, I decided to use only sedatives and to treat the hypertensive patient symptomatically. For the next 3 years, until he left the dispensary, we continued our separate therapies. On days that he was absent I saw his hypertensives, and *vice versa*. The only difference noted between the two groups was that mine were more comfortable, although his patients had a more pronounced lowering of blood pressure. True, the blood cyanate method was not used, but the length of time the patients were kept on the drug seemed sufficient to determine its value. The personal element could be excluded because of the same placid disposition in both, and we had plenty of time. After he left, I "inherited" his hypertensive patients, and thereafter followed all of them. As I could still see no real value to the thiocyanates, I do not use them in the treatment of the hypertensive patients.

Other Drugs. Liver extract[1a,27] was tried in the treatment of such cases, and discarded. I mention it only because an attempt is being made today to revive its use in hypertensives. Among the many other drugs which have been introduced, rapidly discarded, and reintro-

duced one or more times, are curcurbocitrin (watermelon seed),[1b,6,20] calcium lactate,[14] magnesium sulphate by parenteral administration,[45] pancreatic extract,[44] bismuth subnitrate,[3c,11,41] the nitrites,[43b] iodides,[16] xanthine and choline derivatives,[16] hormones,[3d] and garlic-parsley extracts. None of these drugs have any effect whatsoever on the relief of symptoms in the hypertensive patient other than that obtained by the temporary enthusiasm of the administrator.

Vitamin A. The last of the drugs introduced, although it is listed as a food and may be sold in grocery stores, is vitamin A.[35] To date not another reliable report on its use in hypertension has appeared; its value for this purpose remains to be demonstrated.[8]

Experimental Work. The last type of therapy suggested, *but not available*, is the use of parenteral extract of the whole normal kidney.[33a] Because of the occasional shock-like reactions and the lack of standard chemical procedures to yield a uniform product of high potency, it cannot at present be regarded as a practical treatment.[33b] In an extensive report Goldblatt, Kahn and Lewis[22] stated that they tried on dogs with experimental renal hypertension a long list of substances which were used or are still being used in the treatment of human hypertension; and found that there was no significant effect on the blood pressure. Their results with renal extracts of other investigators, as well as with similar extracts of their own preparation, showed either no effect or at the most inconsistent and not very striking lowering of blood pressure in dogs with experimental renal hypertension.

Rational Therapy. How then, if all drugs mentioned have proven of no particular value, shall a hypertensive patient in the pre-cardiac stage be treated. By simply giving him a quiet, non-critical, sympathetic audience, the symptoms can at least be relieved.[28] It seems best not to make any reference to the degree of hypertension, its potential dangers, or its complications. The effect is not one of suggestion; for such patients encouragement about the reduction of the blood pressure is not necessarily good therapy. Many patients need only a good friend with whom they can discuss their troubles. Such difficulties may seem trivial, but are of importance to the patient. A little time, not much, and an unhurried physical examination each visit, with a critical eye on the size of the heart especially, are more assuring to a hypertensive than a non-effective drug.

The only non-toxic drugs, compared with the thiocyanates, used and advised for these patients are mild sedatives, such as phenobarbital and its derivatives in many forms, and a mild laxative such as cascara or rhubarb. By constant observation of many hypertensives I have found nothing as yet which indicates that such an extremely conservative type of optimistic therapy should be altered in the pre-cardiac stage. A sensible hypertensive patient can delay the appearance of the symptoms and signs of heart failure many years with the help of a good friend, his doctor. Symptomatic relief can be given to hypertensives by understanding them and treating them as individuals, rather than just as "cases" of hypertension to be treated by drugs which prove of little benefit.[40]

Credo and Conclusions. When the unpreventable and unpredictable episodes of congestive heart failure, cerebral hemorrhage, coronary thrombosis, or uremia, occur in our hypertensive patients, we can only do our best, which may not be good enough at times. With proper understanding of the individual, we are getting hypertensive patients, except the uremics, back to health far more often than ever before, and with rational care they can and do live out their normal span of life despite the essential hypertension.

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RELATIONSHIP BETWEEN ARTERIOSCLEROSIS OF THE RENAL ARTERY AND HYPERTENSION

Analysis of 100 Necropsies

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Experimentally produced renal ischemia causes a hypertension in dogs and monkeys, which does not persist unless both main renal arteries are constricted. Since the original experimental work,[5] case reports of so-called "Human Goldblatt Dogs" have been published by Leiter,[7] Stewart,[9] Freeman and Hartley,[4] Blatt and Page,[2] Saphir and Ballinger,[8] and others.

In an attempt to compare the experimental results with hypertension in the human, Blackman[1] examined the renal arteries of 50 hypertensive and 50 non-hypertensive individuals. He cut through the point of greatest narrowing after fixation, mounted and stained the sections and then measured the caliber. He found by this method that 86% of the hypertensive cases showed localized narrowing of the arteries varying from moderate to severe in degree of obstruction. Only 10% of the non-hypertensive cases showed partial obstruction. He concluded that the arteriosclerotic changes in the main renal arteries caused sufficient obstruction to induce chronic hypertension by the same mechanism as Goldblatt and others have shown to occur in animals. Blackman's findings have been accepted as explaining hypertension in humans with renal artery occlusion.

The present communication is a report of the condition of the main renal arteries in 100 consecutive cases coming to autopsy at this hospital in which blood pressure readings were obtained. No consistent correlation could be demonstrated between the condition or caliber of the main renal arteries and the presence or absence of hypertension.

The renal arteries attached to the segment of the aorta from which they arose were dissected free throughout their entire length and careful measurements of the arteries and all aberrant branches including the mouths were obtained with graduated sounds. Cross-sections of the vessels were made at the narrowest point. Where no perceptible narrowing existed, sections were taken 1 cm. from the mouth. The tissues were fixed in formalin, cut and stained with hematoxylin and eosin and an elastic tissue stain. The size of the arteries measured according to Blackman's method was compared with the size of the unfixed specimen obtained at the autopsy table. The kidneys were

studied histologically for the presence or absence of vascular changes compatible with hypertension. The hearts were examined histologically for the presence or absence of myocardial hypertrophy.

Among the 100 cases, 56 were hypertensive (31 men, 25 women), and 44 were non-hypertensive (27 men, 17 women). In the entire group there were 58 males and 42 females. The whites numbered 86, the negroes 14, approximately the relative ratio of admission of the two races to the hospital during the period in which this study was carried out. In the hypertensive group, 87.5% were white and 12.5% were black. The ages ranged from 17 to 87 years, the average was 60.3 years. The average age of the hypertensive group was 63.5 years and of the non-hypertensive 55.6 years. Of the 56 hypertensives, 47 were over 50 years of age.

No constant relation could be found between the size of normal non-sclerotic vessels as measured in the unfixed state and the size as found in the fixed stained specimen. Many which had a good caliber when examined at the autopsy table had a degree of contraction which would have justified their inclusion among those with a diminished caliber. Moreover the results were not uniform, so no accurate formula could be used. Because of these results, only the measurements obtained in the unfixed specimens were used for analysis.

Non-sclerotic vessels were regarded as normal. Among the hypertensive cases, 40% of the vessels were of this character. Among the non-hypertensive cases, the incidence was greater, 56.8%. The average diameter of the normal vessels was 4.1 mm. There was no significant difference in those of either group. With hypertension it was 4.1 mm.; with normal tension, 4 mm.

The average diameter of the vessels in all the cases of hypertension was 4 mm., practically the same as was found among the normal vessels in the group. There were only 2 instances of extreme stenosis of the renal arteries from sclerotic deposits simulating the Goldblatt dog. In the non-hypertensive cases, the average diameter of the entire group was also the same as in the non-sclerotic vessels, 4.1 mm. Although these vessels were slightly wider than among the hypertension group, there was no difference when the measurements were corrected for the age factor. Very little correlation between the amount of sclerosis and the degree of constriction of the lumen could be demonstrated. Linear sclerotic plaques caused practically no narrowing. In many instances the severely sclerotic vessels had lumens wider than normal. Although estimations of the cholesterol content of the vessels were not carried out, as was done by Bruger and Chassin,[3] our data suggest that the amount of cholesterol deposited in the vessel wall does not necessarily bear any relationship to its caliber.

The condition of the renal arterioles proved a more reliable guide to the level of the blood pressure reading than the caliber or condition of the extrinsic renal arteries. Goldblatt[5] believed from his experimental work that renal ischemia from obstruction of the renal artery and its associated hemodynamic relationships produced hypertension. On the other hand, Page[6] suggested that the lowering of pulse pressure

within the kidney itself was of more importance than a gross reduction of blood flow. The data obtained from the present study would tend to suppose the latter theory.

Summary and Conclusions. The caliber of the renal arteries was studied in 100 consecutive cases in which blood pressure readings were obtained. Hypertension was present in 56, normal pressures were found in 44. Marked variations were found in the caliber of non-sclerotic vessels when measured in the fresh state and in the fixed stained preparation, therefore, only the figures obtained in the fresh state were used for analysis. The differences of caliber between sclerotic vessels of the hypertensive and non-hypertensive cases were insignificant. Only two instances were found simulating the Goldblatt kidney. The degree of cholesterol deposit bore no relationship to the caliber. The degree and extent of arteriolar sclerosis estimated from the histologic examination of the kidneys proved a better index of the blood pressure readings than the caliber of the main renal arteries. The data lend more support to the theory advanced by Page than that of Goldblatt for the development of hypertension.

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THE SUBCUTANEOUS ADMINISTRATION OF SODIUM SULFATHIAZOLE IN VARIOUS CLINICAL CONDITIONS*

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The clinical efficacy of sulfathiazole in the treatment of certain infectious diseases is established beyond any doubt. The underlying principle of treatment with this drug, as with the other sulfonamides, is the establishment and the maintenance of an adequate concentration of the drug in the blood and the tissue fluids to control the rate of reproduction of the infecting organism. Ordinarily the oral administration of the drug is sufficient to attain and maintain such therapeutic

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blood levels. In certain acute, well-established infectious processes it is an accepted clinical practice to *attain* the therapeutic level rapidly by administering the drug intravenously, and to *maintain* this level by subsequent oral medication.

Occasions arise when the oral administration of the drug constitutes a serious practical difficulty in the clinical management of the patient, or becomes an actual impossibility. The usual procedure, when confronted with such a situation, is to administer the drug, in the form of its sodium salt, intravenously. A serious defect is associated with this approach, for under these circumstances a peak concentration is reached in the blood soon after administration is completed, which rapidly falls off as the drug is excreted. Thus, excessive concentrations are rapidly followed by ineffective levels, and therapeutic effectiveness is far from optimal. The intravenous route is admirable for rapidly disseminating the drug through the body, but it cannot be depended on as the sole method for the treatment of an acute infection.

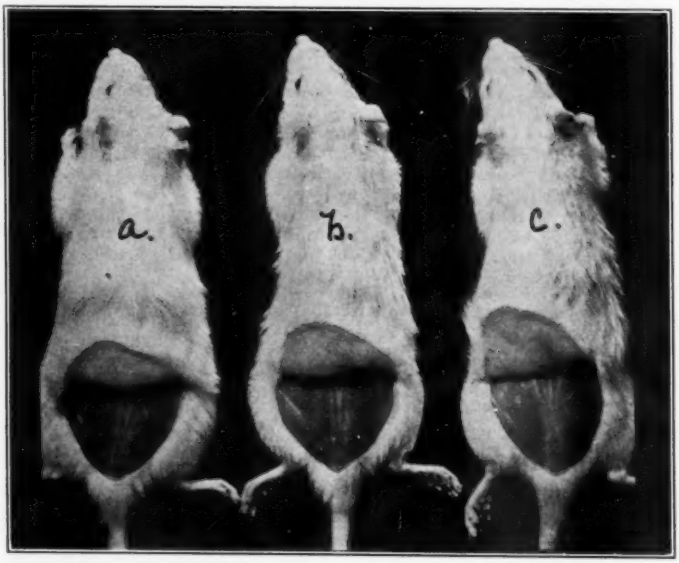

FIG. 1.—Subcutaneous reactions, 24 hours after the subcutaneous administration of 1%, 5%, and 10% aqueous solutions of sodium sulfathiazole. *a*, No reaction. *b*, Slight hyperemia in skin flap. *c*, Marked hyperemia with edema in skin flap.

Some time ago Finland and his co-workers[3] using the water-soluble glucose addition product of sulfapyridine, showed that this compound might be administered subcutaneously without fear of local reactions. Unfortunately, they also pointed out that the glucoside was relatively inert from a therapeutic point of view.[4] Flippin[1] has dealt with the problem by advocating the intramuscular administration of concentrated (33%) solutions of the sodium salt of sulfapyridine.

The pharmacologic evidence presented by Powell and Chen[6] and

by Marshall[5] indicated that the alkaline aqueous solutions of the sodium salts of drugs like sulfapyridine are extremely irritating and that the subcutaneous administration of such solutions might cause severe local reactions or actual tissue destruction. We have found this to be true when concentrations of the order of 10% or higher are administered subcutaneously to experimental animals. We have also observed that such experimental animals tolerate the subcutaneous administration of 1% aqueous solutions of the anhydrous sodium salt of sulfathiazole without showing any sign of tissue reaction, and that only a transient hyperemia results from the subcutaneous administration of a 5% solution.

Figure 1 shows the local reactions in a series of rats to the subcutaneous administration of 0.5 cc. of a 1%, 5%, and 10% solution of sodium sulfathiazole, 24 hours after medication. Animals receiving the 1% solution showed no reaction whatsoever; those receiving the 5% solution showed a slight degree of hyperemia at the end of 24 hours which had practically disappeared at the end of 48 hours, and left no trace whatsoever by the end of 72 hours. The animals receiving the 10% solution showed marked hyperemia and edema at the end of 24 hours which persisted. The lesion became indurated, and involved the subtending fascia by the 72d hour.

Aqueous solutions of the anhydrous sodium salt of sulfathiazole have the following physical properties:

TABLE 1.—PHYSICAL PROPERTIES OF AQUEOUS SOLUTIONS OF SODIUM SULFATHIAZOLE

Concentration	pH	Freezing point depression
0.5	9.55	0.07
1.0	9.72	0.14
5.0	9.8–10.0	0.605
10.0	10.0–10.2	(crystallizes
25.0	10.39	out in cold)

Thus, even 1% solutions are definitely hypotonic; such solutions may be brought to isotonicity by the addition of 0.62% of NaCl. In practice we have neglected this factor and used the hypotonic solutions for subcutaneous injection.

Our clinical evidence agrees with the observations of Taplin and his co-workers[7] and bears out our experimental findings. Up to the present time, more than 200 individuals in the Medical, Gynecological and Surgical Services of the Albany Hospital have received up to 2000 cc. of a 0.5% aqueous solution of sodium sulfathiazole per day, administered subcutaneously at a rate of approximately 100 cc. per hour, without showing a single, serious untoward local reaction. The most serious local reaction encountered in this group of patients was a slight swelling and tenderness of the injection site, which cleared up within a few hours after the application of a hot water bottle. This occurred in 8 patients in our entire series.

The group included all ages: the youngest patient being an infant of 3 weeks suffering from lobar pneumonia, the oldest a man aged 82 suffering from an acute infection of the urinary tract. Figure 2 shows the age distribution of the group.

Sexes were represented almost evenly: 55% females, 45% males. The clinical conditions treated by this method included the usual variety of pathologic states which have shown themselves to be amenable to therapy with this drug, but where oral administration of the drug was either contraindicated or impossible.

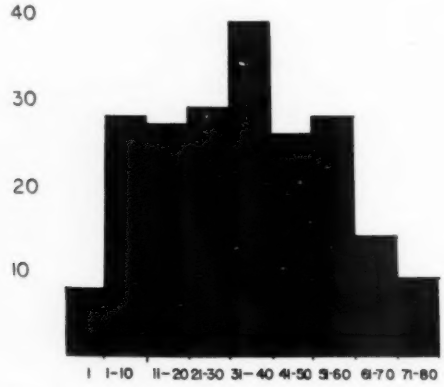

FIG. 2.—Age distribution of patients medicated with subcutaneously administered sodium sulfathiazole.

The following table gives a summary of the clinical results:

TABLE 2.—A SUMMARY OF THE CLINICAL RESULTS

Clinical entities	Total No. of cases	Results	
		Recovered	Died
Acute appendicitis with peritonitis	54	53	1
Pelvic peritonitis	31	31	0
Postoperative hyperpyrexia	25	24	1
Intracranial infections	15	11	4
Postoperative pneumonia	14	11	3
Postoperative peritonitis	11	7	4
Ruptured ulcer with peritonitis	5	3	2
Laryngo-tracheobronchitis	4	0	4
Postoperative urinary tract infections	3	2	1
Lobar pneumonia (complicated)	12	8	4
Puerperal sepsis (including septic abortions)	10	10	0
Post-traumatic infections	6	3	3
Miscellaneous	10	9	1

Infecting organisms included: *Staph. aureus*, *Staph. albus*, Hemolytic streptococcus, non-hemolytic streptococcus, *Strep. viridans*, *B. coli*, *H. influenzæ*, Pneumococci, Types I, II, III, VI, XII, XIII, XV, XIX, XXI, XXII, XXIII, XXV, XXVII, XXIX, XXXII.

Blood concentrations of the drug following this type of medication are somewhat lower than would be expected if the same quantity of the drug had been administered orally. No adequate explanation can be given for this observation at the present time; it may be due to the fact that these individuals were receiving large quantities of parenteral fluids, which would tend to speed up the passage of the drug through the body. This suggestion is substantiated by the small proportion of

acetylated drug which is present in the blood under these circumstances. Following oral administration from 10% to 20% of the drug in the blood is conjugated, while only 5% to 10% is conjugated following subcutaneous administration.

Figure 3 shows the maximum blood concentrations obtained after the subcutaneous administration of 5 gm. of the sodium salt of sulfathiazole in a 12-hour period.

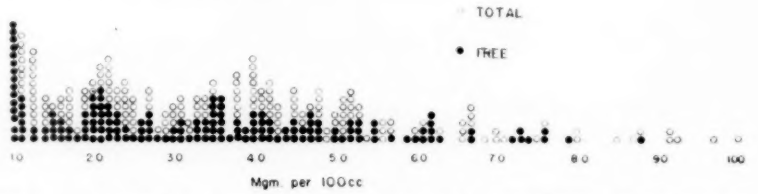

FIG. 3.—Maximum blood concentrations following the subcutaneous administration of 5 gm. of sodium sulfathiazole in 12 hours.

Two cases of complete anuria occurred; both recovered following catheterization of the ureters and the intravenous administration of slightly alkaline buffers. Frank hematuria occurred in 4 instances, while 30 patients showed microscopic crystalluria or occult hematuria. Three patients showed mild secondary anemia.

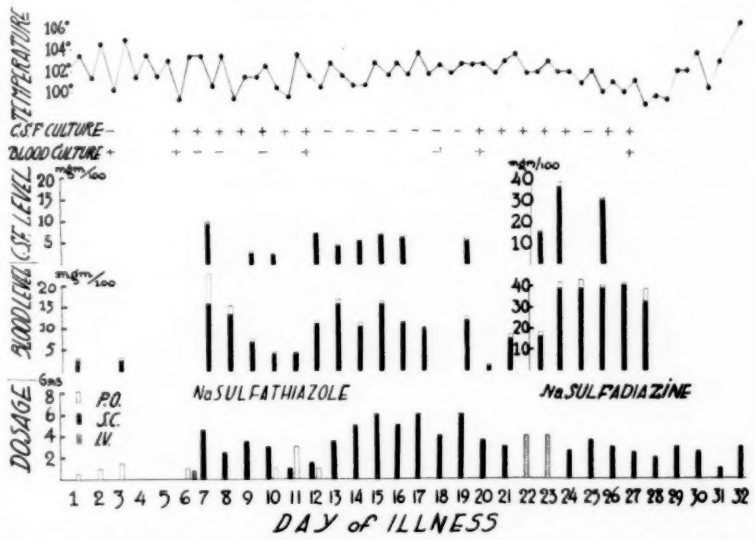

FIG. 4.—A fatal case of *H. influenza* meningitis in an infant. The chart shows, from above down: temperature, cerebrospinal fluid culture, blood culture, cerebrospinal fluid drug content, blood drug content, and dosage.

The incidence of toxic reactions to medication is somewhat higher than would be expected. It should be pointed out, however, that the patients comprising this clinical group were acutely ill; 75% of them had undergone recent major surgical intervention.

Figure 4 diagrammatically illustrates the clinical course of a fatal case of *H. influenzæ meningitis* in an infant. This case is presented in order to demonstrate the blood and cerebrospinal fluid levels attained as a result of the oral, subcutaneous and intravenous administration of sodium sulfathiazole or sodium sulfadiazine. During the early stage of the illness, the administration of the drug was by gavage, but the intestinal distention which resulted from this method of administration made it necessary to resort to some other means of medication. The subcutaneous route was chosen.

During the course of this investigation, sodium sulfadiazine was made available to us. On experimental animals it appeared to be slightly more irritating than the sodium salt of sulfathiazole. However, the administration of equal quantities showed that the sulfadiazine salt gave rise to much higher blood concentrations than did the sulfathiazole salt; this, together with the fact that sulfadiazine traversed the cerebrospinal barrier more readily than does sulfathiazole, led us to try sodium sulfadiazine in the treatment of a number of cases of meningitis. No local reactions were observed. One such case is illustrated where both sodium salts of sulfathiazole and sulfadiazine were employed. In neither instance was there any irritative reaction.

More recently, Jorgensen and Greeley[2] reported on the administration by hypodermoclysis of ½ to 1% solution of sodium sulfadiazine to infants without resulting in a single local reaction. They have used repeated subcutaneous injections of solutions up to 5% without any deleterious reactions.

The chart in Figure 4 illustrates two points to which attention has already been called: (1) Higher blood levels are attained after the administration of sulfadiazine than result from the administration of comparable doses of sulfathiazole. (2) Cerebrospinal fluid concentrations of the drug are much greater after sulfadiazine than they are after sulfathiazole.

Conclusion. The subcutaneous administration of dilute (0.5%) solutions of sodium sulfathiazole afford a safe, practical method for the administration of this drug when oral administration is contraindicated. This conclusion is based upon a study of the physical properties of dilute solutions of sodium sulfathiazole, upon the administration of such solutions to experimental animals, and upon a clinical study of 200 patients who have received sodium sulfathiazole by the subcutaneous route.

The anhydrous sodium sulfathiazole used in this study supplied by Winthrop Chemical Company, New York, N. Y.

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THE THERAPY OF EXPERIMENTALLY INDUCED GANGRENE

PART I. A METHOD OF TESTING LOCAL ANTISEPTICS IN VIVO

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THE primary object of this study was the elaboration of a method for the study of antiseptic action that was based upon *in vivo* experiments. We selected Azochloramid as a presumably effective and safe compound on the basis of many reports which compare its effectiveness with that of other antiseptics, both in bactericidal tests, and in determinations of toxicity (chemotherapeutic) indices.[6,9,10,13]

The development of a technique of producing and treating controlled wound infection in experimental animals has been the goal of many investigations since none of the *in vitro* methods used for the evaluation of local antiseptics permit prediction of their effect in the treatment of wounds.

However, as shown by Reinhardt, Scheimann *et al.* (as described by Browning[2]), also by Kroll *et al.*[8] experimental wounds infected with streptococci either heal spontaneously in a short time, or the infection is so overwhelming that death of the animal is quickly brought about by a septicemia which obviously could not yield to local treatment. Hertz and Hunt[5,7] used *S. aureus* to produce abscesses in mice and hamsters. Healing occurred without treatment in 7 to 8 days; thus the effect of the treatment could not be easily determined.

Somewhat more promising results were obtained when the experimental wound infection was brought about by the use of anaërobic spore-forming organisms. This is largely due to the fact that the infection takes a course slow enough so that an efficient local antiseptic might influence it, and due to the fact that if left untreated, it usually ends fatally, providing an end-point for the control animals. This experimental approach was successfully used by Bliss, Long and Smith.[1]

Since experimental wounds infected with anaërobic bacteria are usually deep and develop tissue necrosis, the treatment requires disinfectants which have penetrating power and activity in the presence of slough and débris. We, therefore, undertook to examine the use of experimentally infected wounds in evaluating a local antiseptic *in vivo*.

Experimental Procedure. Stock cultures of *Clostridium histolyticum*, *Cl. perfringens* and *Cl. septique* were grown in a medium consisting of a veal infusion broth containing 1% proteose peptone, 0.25% dextrose and 1% tryptophane, adjusted to a pH of 7.6. The medium was distributed into large test tubes into which 2 to 3 gm. of finely chopped meat had been placed, which aided in the reduction of the oxygen

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tension of the medium, and furnished additional material for growth. After boiling for 5 minutes to drive out the oxygen and cooling quickly afterwards to prevent reabsorption, the medium was inoculated with 0.5 cc. of the bacterial suspension and sealed with a layer of sterile petrolatum. This method was found to be satisfactory for producing the anaërobic conditions required by the organisms.

The Azochloramid solution used throughout the work was prepared by dissolving 9.45 gm. of the commercially available Azochloramid-salt mixture in 1000 cc. of warm distilled water. The resulting isotonic saline solution contained Azochloramid in a concentration of 1:3300 and was buffered at pH 7.4. The exact concentration of Azochloramid was checked by iodometric titration.

Guinea pigs of approximately the same size, weighing on an average 600 gm. and Syrian hamsters averaging about 120 gm. were used for the experiments. Wounds were produced in the following manner: The animals were anesthetized by injecting 0.3 cc. of nembutal intraperitoneally. The hair of the leg and back was removed by clipping, the thigh washed with alcohol and the skin and muscle of the thigh were then bruised by pinching with a heavy sterile forceps. This resulted in the formation of a slightly edematous contused area of about 0.5 cm. in diameter. Care was taken not to break the skin. The infection was produced by immediately injecting into this bruised area 0.5 cc. of a broth culture of *Cl. histolyticum*, or of a mixture of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septique* cultures. In order to preclude too rapid development of an overwhelming infection, the injection was made superficially. When the culture of a single organism was injected the infections were well established after 15 to 20 hours. They were characterized by marked swelling and stiffening of the leg, lysis, destruction and sloughing of the skin over the area of the wound, which, at this stage, had increased to about 2.5 cm. in diameter. The muscles were pale pink in color. In other groups of animals the gangrenous lesions were produced by inoculating with 0.5 cc. of a mixed culture of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septique*. The lesions were of similar appearance as the ones produced by *Cl. histolyticum* alone but appeared sooner, approximately 10 hours following the infection.

In the control animals the lesions continued to increase in extent until the whole lower leg became involved. In most cases these animals died on the 3d or 4th day due to invasion of the abdominal cavity followed by peritonitis. In some instances, this was preceded by complete destruction and lysis of the tissue of the leg and thigh, leaving the bone exposed.

In the test animals, treatment with the antiseptic was instituted 15 to 20 hours after the injection of the single culture, or 10 hours after the injection of a mixed culture, when active lesions showing necrosis and edema had been well established. The animals were anesthetized with nembutal. The wound area was irrigated and washed with cotton swabs saturated with the aqueous solution of Azochloramid. After the wounds were cleaned a wet dressing con-

sisting of a pledget of cotton saturated with the Azochloramid solution was applied in such a way that good contact was maintained with all parts of the affected region. No attempt was made to bandage the leg with gauze or tape as the animals have a tendency to tear at them until they come off and, in so doing, might enlarge or contaminate the lesions with other organisms. The wet dressing was allowed to stay in contact with the wound for as long a period as the anesthetic kept the animal quiet, usually several hours.

This treatment was carried out twice daily for 3 to 4 days, during which time a heavy scab formed over the wound. Following this, the applications of Azochloramid were reduced to one a day for 3 to 4 days; then the wound was allowed to heal without further attention. Usually, the first scar and large amounts of dead tissue had sloughed off within 14 days, a thinner, lighter colored scab having formed beneath. In most cases, complete recovery occurred in about a month with only a small scar remaining. (Table 1.)

In some of these experimental infections in guinea pigs it was also decided to test the effect of a wetting agent, sodium tetradecyl sulfate (sodium 2-methyl 7-ethyl undecanol-4 sulfate) along with Azochloramid. The difference in the time of healing of the wounds does not seem to be significant (Table 1).

TABLE 1.—EFFECT OF TREATMENT WITH AZOCHLORAMID ON EXPERIMENTALLY INFECTED WOUNDS IN GUINEA PIGS

Infections	Treatment	Animals, No.	Recovered	Deaths	Recovered, %
Cl. histolyticum	None	7	1	6	14
Cl. histolyticum	Azochloramid	22	20	2	91
*Cl. histolyticum**	None	11	1	10	9
*Cl. histolyticum**	Azochloramid	21	15	6	71
*Cl. perfringens** *Cl. septique**	Azochloramid and wetting agent	9	8	1	89
	None	5	1	4	20

* Mixed culture.

Experimental infections were also produced in Syrian hamsters. In view of the smaller size of these animals, the amount of bacterial suspension injected was reduced to 0.2 cc. Typical lesions described above were produced in 15 to 20 hours and the treatment was carried out in the same manner and to the same extent as with the guinea pigs.

A group of hamsters was infected with the mixed culture of organisms and, although the lesions developed more rapidly, the severity of the acute infection was overcome in about 8 to 10 days. The wounds healed completely in about 3 weeks leaving only a small scar (Table 2).

TABLE 2.—EFFECT OF TREATMENT WITH AZOCHLORAMID OF EXPERIMENTALLY INFECTED WOUNDS IN SYRIAN HAMSTERS

Infection	Treatment	Animals, No.	Recovered	Deaths	Recovered, %
Cl. histolyticum	Azochloramid	13	11	2	85
Cl. histolyticum	None	5	1	4	20
*Cl. histolyticum** *Cl perfringens** *Cl. septique**	Azochloramid	10	9	1	90
	None	5	0	5	0

* Mixed culture.

Controls were used with each group of animals undergoing treatment. These controls were infected in the manner described, some received no treatment whatever, while others were treated with sterile saline following the procedure outlined for Azochloramid in the test animals. The saline treatment had no effect on the course of the infection.

During the course of treatment of the infected wounds of both guinea pigs and hamsters, the types of organisms present were studied by making smears of some of the edematous material of each lesion at 2-day intervals. Following 4 to 6 days' treatment the organisms had disappeared from the wounds. In several animals staphylococci were found, but none were seen in stained preparations from the lesions of treated animals made 1 or 2 days after their appearance if treatment was continued.

Conclusions (Part I). Experimentally induced gangrene was produced in guinea pigs and Syrian hamsters either with *Cl. histolyticum* or with mixtures of cultures of *Cl. histolyticum*, *Cl. perfringens* and *Cl. septique*. The infections in the test animals were treated with a stock solution of Azochloramid or with Azochloramid combined with a wetting agent, sodium tetradecyl sulfate. Of this group there were 71 to 91% recoveries as compared with an 80 to 100% mortality in the control animals. In these experiments there was no significant difference between the action of Azochloramid itself and that containing a wetting agent; each gave good results when used in treatment of the gangrenous lesions in guinea pigs.

The results of the experiments demonstrate the marked effect of Azochloramid when used as a therapeutic agent on gangrenous wounds in animals. The severity of the infections with *Cl. histolyticum* was quickly reduced by daily treatments with Azochloramid for a period of 10 days, and complete healing of the wounds in both guinea pigs and hamsters resulted within 1 month. Similar results were obtained in the treatment with Azochloramid of experimentally induced wounds with mixed cultures of *Cl. perfringens*, *Cl. histolyticum* and *Cl. septique*.

These therapeutic effects are undoubtedly due to the ability of Azochloramid to destroy and inactivate the toxins and lysins of these anaërobes in concentrations far below those required to inhibit growth.

Part II. The Effect of Azochloramid on Various Anaërobic Bacteria and Their Toxins

Anaërobic bacteria, common inhabitants of the soil, are not infrequently encountered in traumatic and war wounds. Although they have little invasive ability, their toxins damage the surface tissue by destruction and lysis. Of this group of anaërobic bacteria those associated with gas gangrene, botulism and tetanus are the most important.

The effect of an antiseptic on the growth, hemolysins and lethal toxins of this group of bacteria was considered of interest. An investigation was made to determine the efficacy of Azochloramid (N,N′-

Dichloroazodicarbonamidine),[11] a chlorine compound deriving its bactericidal effect from the slow release of hypochlorous acid in a water solution. Its advantage over other chlorine compounds lies in its stability in the presence of extraneous organic matter. Guiteras and Schmelkes[3] have shown that Azochloramid reacts with amino acids and proteins only to a slight extent under conditions where the other chlorine compounds are easily inactivated.

Since this work was started, Heise and Starin[4] have reported similar studies with staphylococci.

Experimental Procedure. The organisms used in these studies were 3 strains of *Cl. perfringens*, and 1 strain each of *Cl. histolyticum*, *Cl. tetani*, *Cl. botulinum* and *Cl. septique*.

The medium for culture and toxin production of these organisms is the same as that described in Part I. The crude toxins used in all tests were obtained by filtering the broth cultures through Berkefeld "V" candles.

For the tests to determine the inhibiting power of Azochloramid on growth and toxin production of these organisms, solutions of Azochloramid were added directly to the culture tubes so that each tube contained a definite concentration ranging from 1:3300 to 1:33,000. The tubes were then inoculated with 0.5 cc. of a heavy suspension of the organism, immediately sealed with sterile petrolatum, and incubated for 24 hours at 37.5° C. Growth was determined by the turbidity of the culture tubes after 24 hours and subcultures were made for confirmation.

The presence of hemolysins was determined by filtering the 24-hour broth cultures through Berkefeld "V" candles and using this filtrate as follows:

Red blood cells obtained from horse, sheep, rabbit and human blood were centrifuged and washed 3 times with physiologic saline solution. A 3% cell suspension was then made up in saline buffered at a pH of 7.4. One cc. quantities of the filtrate were distributed in small test tubes; 0.5 cc. of the 3% cell suspension was added to each tube, and the volumes were brought to 2.5 cc. with buffered saline. The tubes were well shaken and incubated in a water-bath for ½ hour at 37.5° C. The final results were read after storing the tubes in a cold room for 24 hours.

The presence of lethal toxins in the filtrates from the cultures which grew in the presence of Azochloramid was determined by intravenous injection of 0.2 cc. of the filtrate into mice. The mice used were of a standard age of 12 weeks.

The effect of Azochloramid on preformed hemolysins produced by the various groups of anaërobes when grown under optimum conditions were studied. The organisms were grown until the maximum quantity of hemolysins was obtained. The filtrates from these broth cultures were titrated with erythrocytes to determine the concentration of hemolysin produced by each organism. The highest dilution of hemolysin producing 50% hemolysis was taken to be the minimal hemolytic dose (m.h.d.).

Multiple series of dilutions of Azochloramid-salt mixture were prepared. To each series was added 1 cc. amounts of each filtrate containing known multiple m.h.d. The tubes were well shaken, then incubated in a water-bath for ½ hour at 37.5° C. At the end of this time 0.5 cc. of a 3% suspension of red cells was added to each tube and they were again shaken and incubated for ½ hour. The tubes were placed in the cold room and a final reading for hemolysis was made after 24 hours.

A study was made of the action of Azochloramid on the lethal toxins as produced by the organisms in artificial culture medium under optimum conditions. The minimal lethal dose (m.l.d.) for mice of the toxic filtrates of the different organisms was carefully determined. One m.l.d. for mice was the amount of toxin that would kill mice of standard size and age in 24 hours when injected intravenously. The effect of Azochloramid on these toxins was determined by mixing 1 cc. amounts of toxin containing multiple m.l.d. with Azochloramid. Each tube containing these mixtures was well shaken and placed in a water-bath for ½ hour at 37.5° C., after which 0.2 cc. of each toxin-Azochloramid mixture was injected intravenously into mice.

Complete protection of the treated animal was the arbitrarily selected criterion of the inhibitory potency of Azochloramid against the lethal toxin. The protective value was expressed in terms of the amount of Azochloramid that would protect the mouse against the multiple m.l.d. injected. As the toxin of *Cl. botulinum* is so much more potent than those of the other anaërobes studied, a special test was carried out with it as follows: 1 cc. amounts of the stock Azochloramid-salt solution (1:3300) were added to 1 cc. of diluted toxin. These dilutions contained between 100 to 4000 m.l.d. The tubes were well shaken, then incubated in a water-bath for ½ hour at 37.5° C. Following this 0.4 cc. of each mixture was injected intravenously into mice.

Results. The results obtained when Azochloramid is incorporated in the culture medium are indicative of its inhibiting action on the growth of the different bacterial species. The concentration of Azochloramid necessary to cause complete inhibition of growth varies; *i. e.*, *Cl. perfringens* was completely inhibited by a dilution of 1/5280; *Cl. histolyticum* by 1/6600; *Cl. tetani* by 1/8250; *Cl. botulinum* by 1/4720, and *Cl. septique* by 1/5280. These are the minimum concentrations preventing growth in the culture tubes. Such negative observations were always confirmed by subcultures (Table 3).

The development of hemolysins for different types of erythrocytes was also inhibited by Azochloramid in the medium (Table 3). This reaction was prevented by lower concentrations of Azochloramid than those required to prevent growth. Effective concentrations range between 1/5280 for *Cl. botulinum* to 1/8250 for the other anaërobes studied. No variation was noted with respect to the inhibition of the hemolysins for the erythrocytes of the different species.

The production of lethal toxin was similarly inhibited by the presence of Azochloramid in the culture medium. Examination of the data in Table 3 shows that in most instances inhibition of formation of the

lethal toxins is brought about with even lower concentrations of Azochloramid than inactivation of hemolysins. Effective concentrations range between 1/8250 for *Cl. histolyticum* to between 1/16,500 and 1/33,000 for the various strains of *Cl. perfringens*.

TABLE 3.—THE INHIBITION OF HEMOLYSIN, LETHAL TOXIN AND GROWTH WHEN AZOCHLORAMID WAS INCORPORATED IN THE CULTURE MEDIUM

		Dil. of Azochloramid in medium preventing					
		Hemolysin production				Lethal toxin	
Organism	Strain	Horse	Sheep	Rabbit	Human	production	Growth
Cl. perfringens	O.S.B.H.	1:8250	1:8250	1:8250	1:8250	1:33,000	1: 5,280
Cl. perfringens	Hall	1:8250	1:8250	1:8250	1:8250	1:16,500	1: 5,280
Cl. perfringens	Novy	..	..	..	..	1:33,000	1:10,890
Cl. histolyticum	Spray	1:8250	1:8250	1:8250	1:8250	1: 8,250	1: 6,600
Cl. tetani	O.S.U.	1:8250	1:8250	1:8250	1:8250	..	1: 8,250
Cl. botulinum	M_7A_2	1:5280	1:5280	1:5280	1:5280	*	1: 4,720
Cl. septique	O.S.U.	1:8250	1:8250	1:8250	1:8250	1:16,500	1: 5,280

* Where growth occurred when *Cl. botulinum* was cultured in the presence of Azochloramid a lethal toxin could always be demonstrated.

The hemolysins used in this study were produced by growing the organisms under anaërobic conditions in the artificial medium previously described for the time required to produce the maximum yield. The results indicate that Azochloramid has a marked effect on hemolysins even in low concentrations. As a uniform volume of filtrate was used throughout the experiment and the potency of the hemolysin for the different organisms varied between 10 m.h.d. and 20 m.h.d. per cc. the concentration of Azochloramid necessary to inactivate the different hemolysins was not strictly comparable. The concentrations of Azochloramid capable of reducing the hemolytic titres are quite low, ranging between 1/16,500 and 1/33,000 when tested against multiple m.h.d. (Table 4).

TABLE 4.—THE EFFECT OF AZOCHLORAMID ON THE HEMOLYSINS OF VARIOUS ANAËROBIC BACTERIA

			Dil. of Azochloramid which completely inhibits the lysis of cells			
Organism	Strain	No. of m.h.d. in 1 cc.	Horse	Human	Sheep	Rabbit
Cl. perfringens	O.S.B.H.	20	1:26,400	1:26,400	1:26,400	1:26,400
Cl. perfringens	Hall	20	1:26,400	1:26,400	1:26,400	1:26,400
Cl. histolyticum	Spray	10	1:33,000	1:26,400	1:33,000	1:26,400
Cl. tetani	O.S.U.	10	1:26,400	1:33,000	1:26,400	1:26,400
Cl. botulinum	M_7A_2	8	1:33,000	1:33,000	1:33,000	1:33,000
Cl. septique	O.S.U.	15	1:16,500	1:16,500	1:16,500	1:16,500

The preformed lethal toxins used in this investigation were produced by growing the various anaërobes under optimum conditions for the length of time necessary for the production of a maximum yield of potent toxin. The results of these experiments demonstrate the marked effect of low concentrations of Azochloramid on the lethal toxins of the organisms studied. The amount of lethal toxin used varied with the different organisms since a constant volume of toxic filtrates was used throughout these experiments. The titres of different toxins varied from 8 m.l.d. for *Cl. perfringens* (Novy strain) to 100,000 m.l.d. per cc. for *Cl. botulinum*. Therefore, again the minimum inhibiting concentrations of Azochloramid are not strictly comparable.

The protective value of Azochloramid was defined as that amount which would react with the toxin in such a way as to render it inactive when multiple m.l.d. were injected into the mice. The results show, as may be seen in Table 5, that low concentrations of Azochloramid have the capacity to inactivate the lethal toxins even when multiple m.l.d. are injected. The dilutions of Azochloramid inactivating these toxins ranged from 1/16,500 for the 3 strains of *Cl. perfringens* and *Cl. septique* to 1/33,000 for *Cl. histolyticum*. The m.l.d. per cc. of the lethal toxins varied a great deal but the same high dilution of Azochloramid had an equal effect on the multiple m.l.d. of each toxin. The toxin of *Cl. botulinum* was an exception in this test when the same procedure was followed as with the other toxins. When 1 volume of this toxin containing 100,000 m.l.d. was mixed with an equal volume of a standard saline solution of Azochloramid (1:3300) the toxic filtrate was not inactivated as the injected mice died in the same time as the controls.

TABLE 5.—THE EFFECT OF AZOCHLORAMID ON THE LETHAL TOXINS OF VARIOUS ANAËROBIC ORGANISMS

Organisms	Strain	No. of m.l.d. in 1 cc.	Dil. of Azochloramid that protected mice from multiple m.l.d. of toxin
Cl perfringens	O.S.B.H.	15	1:16,500
Cl. perfringens	Hall	20	1:16,500
Cl. perfringens	Novy	8	1:16,500
Cl. histolyticum	Spray	20	1:33,000
Cl. botulinum	M_7A_2	100,000	No protection
Cl. septique	O.S.U.	17	1:16,500

Therefore, a special experiment was set up to determine the largest number of m.l.d. against which the stock solution of Azochloramid was effective. The results of this test, as seen in Table 6, show that a dilution of 1/3300 of Azochloramid will protect mice against a maximum of 250 m.l.d. of the *Cl. botulinum* toxin.

TABLE 6.—THE EFFECT OF AZOCHLORAMID ON CL. BOTULINUM TOXIN

M.l.d.	Amt. toxin	Azo. (1/3300)	Incub.	Amt. inject.	Survival time (in days) 1	2	3	4	5
100	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	+	+	+	+	+*
250	1 cc	1 cc.	½ hr. 37.5° C.	0.4 cc.	+	+	+	+	+*
500	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	+	−			
750	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	−				
1000	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	−				
1500	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	−				
2000	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	−				
4000	1 cc.	1 cc.	½ hr. 37.5° C.	0.4 cc.	−				

+ = living, − = died, * = complete protection.

Conclusions (Part II). 1. Low concentrations of Azochloramid (1/4720 to 1/10,980) when incorporated in the culture medium inhibit the growth of various groups of anaërobic bacteria.

2. The production of hemolysins and lethal toxins of these organisms in the culture medium is inhibited by even lower concentrations of Azochloramid (1/5280 to 1/33,000).

3. When acting upon filtrates of these organisms, similarly low con-

centrations of Azochloramid inactivate appreciable amounts of preformed hemolysins and lethal toxins.

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STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERIZINE, SULFAMETHYLDIAZINE) IN MAN*

I. Absorption, Distribution, and Excretion

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The disadvantages associated with the sulfonamide drugs now in common use have led to an increasing search for an improved derivative. In an attempt to find a more satisfactory sulfonamide, we have interested ourselves in sulfamerizine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine), the methyl homologue of sulfadiazine, which has been synthesized by several groups of investigators.[2,6,7] The therapeutic activity of sulfamerizine was described by Roblin *et al.*[6] at the same time that they reported on sulfadiazine and it was shown that in preliminary mouse tests both of these drugs were considerably more active against streptococcal, pneumococcal, and staphylococcal infections in mice than sulfanilamide, sulfapyridine, or sulfathiazole. Pharmacologic studies in various species of laboratory ani-

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mals,[8] and humans[3,8] have indicated that sulfamerizine is more rapidly and more completely absorbed from the gastro-intestinal tract than sulfadiazine. Furthermore, it was shown by Welch *et al.*[8] that sulfamerizine and its acetyl derivative were more soluble in urine than sulfadiazine and acetylsulfadiazine. Further studies by this group[8] suggested that sulfamerizine is no more toxic in experimental animals than sulfadiazine when a comparison is made on the basis of blood concentration of the drugs.

The present report offers certain observations dealing with the absorption, distribution, and excretion of sulfamerizine* in humans. Two groups of experiments were conducted, those in which a single dose of the drug was administered orally, subcutaneously, intravenously, or rectally, and those in which multiple doses were administered over a period of days.

Methods and Materials. Sulfamerizine was determined by the method of Bratton and Marshall[1] with the exception that para-toluene-sulfonic acid was used as protein precipitant for most of the work in place of trichloracetic acid. Studies on acetylated sulfamerizine in blood have shown that from 5% of the drug at low concentrations to 15% at higher concentrations is not recovered by this method and we have corrected our results accordingly; the slight loss may be due to adsorption of the drug during blood protein precipitation. Determinations of sulfamerizine were made on serum because of the variability in the amount of drug found in the red blood cells when whole blood is used. The fate of a single dose of sulfamerizine, administered by various routes, was studied in 16 patients who were selected on the basis of normal gastro-intestinal, hepatic, and renal function and were for the most part young healthy males convalescing from minor surgical procedures. No attempt was made to determine the exact fluid intake but it approximated 1500 to 2000 cc. in 24 hours. The 21 patients in whom body fluid concentrations were studied fell into no specific category and varied from healthy to seriously ill individuals. Continuous administration of sulfamerizine was studied in 15 patients suffering from a variety of diseases, including pneumococcal pneumonia, meningococcal meningitis, hemolytic streptococcal cellulitis and subacute bacterial endocarditis.

Results. A. Absorption and Excretion of Sulfamerizine. I. *Fate of a Single Oral Dose* (Table 1). Eight (Nos. 1, 2, 3, 4, 5, 6, 7, and 8) young male patients were given 3 gm. of sulfamerizine by mouth. Blood specimens were taken at appropriate intervals and urine collected over 24- and 48-hour periods. At the end of 2 hours the average concentration of free sulfamerizine in the serum was 12.8 mg. per 100 cc. and it continued to rise so that after 4 hours the average concentration reached a peak of 13.4 mg. per 100 cc. of free drug. Thereafter the level began to fall and at the end of 24 hours it averaged 5.9 mg. per 100 cc. of free drug. Acetylation of the drug varied somewhat, but reasonable values were obtained. During the first 6 hours an average of 8.7% of the total drug was in the acetylated form. However, in the 12- to 24-hour period the average amount of acetylated drug increased to 15%. At the end of 48 hours no acetylation was evident in 5 of the 8 subjects.

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TABLE 1.—FATE OF SULFAMERIZINE ADMINISTERED BY VARIOUS ROUTES

Absorption and Excretion of Single Oral Dose (3 Gm.) of Sulfamerizine

				Amount of sulfamerizine						
				Serum			Urine				
No.	Patient Age (yrs.) Wt. (lbs.)	Time (hrs.)		Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Cumulative excretion (%)	Urine vol. (cc.)
1	W. H.	2		12.6	13.7	8.0					
	19	4		12.4	13.1	5.6					
	160	6		10.9	12.5	11.4					
		12		8.6	9.3	7.5					
		24		7.2	8.0	10.0	32.0	47.0	31.9	38.3	2450
		48		3.5	3.2	..	17.4	30.8	43.5	60.3	2150
2	H. K.	2		13.4	15.3	12.4					
	34	4		15.2	17.6	13.7					
	132	6		13.6	16.2	16.0					
		12		9.2	11.2	17.9					
		24		4.9	5.3	7.5	28.4	62.8	54.8	56.0	2675
		48		1.5	1.4	..	12.0	31.0	61.3	72.0	1550
3	G. N.	2		14.7	15.4	4.5					
	23	4		15.5	16.9	8.3					
	150	6		15.4	16.7	7.8					
		12		8.5	12.6	32.5					
		24		7.2	9.0	20.0	88.0	138.0	36.2	70.3	1530
		48		2.6	2.5	..	23.0	42.0	45.2	87.3	1200
4	H. L.	2		12.1	12.6	3.9					
	24	4		12.8	13.8	7.2					
	135	6		11.3	11.0						
		12		8.3	9.1	8.8					
		24		6.5	7.1	8.4	42.5	93.8	54.7	32.0	1040
		48		1.9	2.0	5.0	37.4	100.0	63.6	60.3	850
5	J. D.	2		19.1	20.8	8.1					
	20	4		17.3	19.2	9.5					
	145	6		14.9	16.3	8.6					
		12		9.0	9.9	9.1					
		24		3.6	4.7	23.4	136.0	292.5	53.5	61.4	630
		48		0.6	0.6	..	18.0	36.5	50.6	71.3	810
6	A. K.	2		8.2	8.8	6.2					
	23	4		10.1	11.5	12.2					
	125	6		11.9	13.5	11.9					
		12		10.5	12.2	13.7					
		24		5.6	7.5	25.3	27.0	31.3	14.1	25.2	2420
		48		2.7	2.9	6.2	31.6	56.8	44.4	49.4	1280
7	C. C.	2		12.0	13.0	7.7					
	64	4		13.3	14.2	6.3					
	165	6		12.0	13.3	9.8					
		12		9.8	10.9	10.2					
		24		6.3	6.9	8.7	31.0	38.1	18.7	16.1	1265
		48		2.3	2.3	..	24.2	42.4	42.9	35.4	1370
8	D. S.	2		10.5	11.4	7.9					
	17	4		10.7	11.8	9.3					
	147	6		10.4	11.4	8.8					
		12		7.8	8.5	8.2					
		24		6.1	6.9	11.6	50.5	77.5	34.8	21.6	850
		48		2.7	2.8	3.5	32.0	66.4	51.8	31.7	440
	Absorption of Single Rectal Dose (3 Gm.) of Sulfamerizine										
9	M. R.	2		tr.	tr.						
	40	4		tr.	tr.						
	135	6		tr.	tr.						
		12		1.0	1.0						
		24		tr.	tr.						
10	A. E.	2		tr.	tr.						
	25	4		tr.	tr.						
	124	6		tr.	tr.						
		12		tr.	tr.						
		24		tr.	tr.						
	Absorption and Excretion After Parenteral Administration of Sulfamerizine—Intravenous Injection of Single 3 Gm. Dose of Sulfamerizine Sodium (5%) Solution										
11	E. C.		½	19.3	20.5	5.9					
	17	2		14.3	15.2	5.9					
	122	4		13.4	14.9	10.1					
		6		12.1	12.9	6.0					
		12		10.3	11.6	11.2					
		24		5.7	6.0	5.0	30.2	60.4	50.0	26.0	1290
		48		1.9	1.9	..	12.0	72.2	83.4	47.6	900
12	T. F.		½	20.0	21.2	5.7					
	24	2		17.7	18.5	4.3					
	122	4		14.4	16.2	11.1					
		6		12.0	13.9	13.7					
		12		9.2	10.5	12.4					
		24		4.0	3.9	..	58.0	164.0	64.7	69.7	1265
		48		0.8	0.5	..	5.4	29.6	81.8	80.0	1050

TABLE 1.—(*Continued.*)

				Amount of sulfamerizine						
			Serum			Urine				
No.	Patient Age (yrs.) Wt. (lbs.)	Time (hrs.)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Cumulative excretion (%)	Urine vol. (cc.)
Subcutaneous Infusion of Single 3 Gm. Dose of Sulfamerizine Sodium (0.5% Solution)										
13	N. G.	2	9.8	10.7	8.4					
	35	6	13.7	15.3	10.4					
	145	12	11.3	12.9	12.4					
		24	7.5	9.2	18.6					
14	F. E.	2	12.5	13.6	8.1					
	51	6	13.3	15.5	14.2					
	145	12	11.1	13.6	19.0					
		24	8.3	10.5	20.9					
15	L. N.	2	11.5	13.0	11.5					
	37	6	12.5	11.8						
	140	12	8.5	10.2	16.6					
		24	4.0	4.6	13.0					
16	J. D.	2	15.0	16.5	9.1					
	33	6	14.0	15.7	10.9					
	133	12	10.8	12.7	14.9					
		24	4.8	6.0	20.0					

Urinary excretion of the drug was measured. Within 24 hours an average of 40.1% of the ingested drug was found in the urine, while after 48 hours only 58.5% had been excreted through the urinary tract. The figures varied from 31.7% in 48 hours to 87.3% in the same length of time. One patient (No. 7), 65 years of age, excreted only 16.1% in 24 hours and 35.4% in 48 hours. During the first 24 hours an average of 37.3% of the excreted drug was in the acetylated form. After 48 hours, however, 50% was acetylated drug.

II. *Fate of a Single Rectal Dose* (Table 1). Two females (Nos. 9 and 10) were given 3 gm. of sulfamerizine in aqueous suspension by retention enema and absorption was studied. At no time was more than a trace of the drug found in the blood.

III. *Fate of a Single Intravenous Dose* (Table 1). Two young males (Nos. 11 and 12) were each given 3 gm. of sulfamerizine sodium in 5% solution in sterile distilled water intravenously. Within ½ hour the average level of free drug was 19.6 mg. per 100 cc.; in 2 hours the concentration averaged 16 mg.; at the end of 4 hours, 13.9 mg.; at the end of 24 hours 4.8 mg. per 100 cc.

IV. *Fate of a Single Subcutaneous Dose* (Table 1). Four males (Nos. 13, 14, 15, and 16) were each given 3 gm. of sulfamerizine sodium, 0.5% concentration in 0.85% saline solution, subcutaneously. Blood specimens were taken at appropriate intervals following administration. In 2 hours the average concentration of free drug was 12.2 mg. per 100 cc., reaching a peak in 6 hours of 13.4 mg., and falling off to 6.2 mg. in 24 hours. Acetylation very closely paralleled that found with the oral administration; about 7% of the total drug in the first 6 hours was acetylated, while in the 12- and 24-hour periods the average acetylation was approximately 16.5%.

V. *Multiple Dosage* (Table 2). Fifteen patients (Nos. 17 to 31, inclusive), suffering from several diseases, including pneumococcal pneumonia, meningococcal meningitis, subacute bacterial endocarditis, and hemolytic streptococcal cellulitis, were treated with sulfamerizine for varying periods of time and with different dosage schedules. Most

of these received an initial dose of from 2 to 3 gm. These patients were divided roughly into four groups: (1) given 1 gm. of sulfamerizine every 6th hour; (2) received 1 gm. every 8th hour; (3) received 1 gm. every 12th hour; (4) 2 patients who received massive intravenous dosages. Variance of the serum concentration of the drug from person to person in the same dosage group was observed and in several instances the degree was marked. In some of these this was obviously the result of change of dosage on clinical indication. In others we have thought it to be due in part to differences in body weight and fluid balance. However, in the same individual the levels were constant. It should be stated, also, that due to the various dosage schedules and hospital routine, the time interval separating the last dose and withdrawal of the blood specimen could not be kept constant in all instances, as these patients were under active treatment for acute infections.

The patients (Nos. 17, 18, 19, 20, and 27) who received 1 gm. of sulfamerizine every 6 hours maintained an average serum concentration of free drug of 13.8 mg. per 100 cc. Levels ranged from 4.7 to 20.5 mg. per 100 cc. In this group the concentration of acetylsulfamerizine averaged 11% of the total drug. The group (Nos. 21, 22, 23, 24, 25, and 26) receiving 1 gm. of the drug at 8-hour intervals showed an average serum concentration of 11.3 mg. per 100 cc. of free drug (range, 3.9 to 19.6 mg.). About 18% of the total drug was in the acetylated form. Two patients (Nos. 28 and 29) received 1 gm. of sulfamerizine every 12 hours. The average level of free drug in the serum was 10.5 mg. per 100 cc. (range, 8.9 to 13.3 mg.). Acetylation in this group averaged 10.2% of the total drug.

Two patients (Nos. 30 and 31) suffering from subacute bacterial endocarditis received large intravenous doses of sulfamerizine sodium. One, a young white male, weighing 154 pounds (70 kg.) received 14 gm. of sulfamerizine by mouth in the first 3 days to check sensitivity. On the 4th day he was given 25 gm. of sulfamerizine sodium intravenously as a 5% solution in sterile distilled water. This solution was given over a 2-hour period. One hour after the infusion had been completed the serum concentration of free sulfamerizine was 106 mg. per 100 cc. Eleven hours later the level had fallen to 79.4 mg. per 100 cc. After 6 days the level was 2 mg. per 100 cc. Nausea was troublesome for several days and it is of interest to note that vomitus obtained 3 days after the last oral dose of the drug and 2 days after the massive intravenous dose contained sulfamerizine in relatively high concentration. The second patient, a young white female who weighed 90 pounds (40 kg.) was managed in the same fashion with the exception that she received 15 gm. of sulfamerizine sodium intravenously. One hour after the end of the infusion her serum concentration of free drug was 90.4 mg. per 100 cc. In 12 hours this had fallen to 73.2 mg. per 100 cc.

A study of the daily urinary excretion of 2 patients receiving 4 gm. of the drug per day showed concentrations of free sulfamerizine ranging from 8.4 to 162.5 mg. per 100 cc. and total sulfamerizine from 18.4 to

TABLE 2.—EFFECT OF CONTINUED ORAL ADMINISTRATION OF SULFAMERIZINE

			Sulfamerizine							
				Serum			Urine			
No.	Patient Age (yrs.)	Day	Dose (gm.)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Daily excretion (gm.)
17	H. A. 33	1	4	...	...	...	8.4	18.4	54.3	0.08
		2	4	15.5	16.8	7.7	38.6	45.0	16.4	1.04
		3	4	20.4	21.8	6.4	162.5	191.3	15.0	2.09
		4	4	19.4	20.3	4.4	114.5	153.8	25.5	2.54
		5	4	17.9	19.3	7.2				
		6	4	18.4	19.9	8.2				
		7	4	16.1	17.4	7.5				
		8	3	16.5	18.3	9.8				
		9	3	16.4	17.8	7.8				
18	N. D. 28	1	4							
		2	4	5.9	6.7	11.9				
		3	4	8.9	9.8	9.2	32.0	92.4	64.9	1.63
		4	4	12.0	13.6	11.8	56.0	151.2	62.9	1.39
		5	4	10.9	13.1	16.7	44.2	127.5	65.3	2.68
		6	4	9.7	11.7	17.0	54.6	147.5	62.9	3.30
		7	4	4.7	5.2	9.6	44.6	140.0	68.1	2.88
		8	4	9.8	12.5	21.6	...	41.5	...	1.17
		9	0	3.5	3.9	10.3	40.0	145.0	72.4	2.12
19	H. M. 17	1	2							
		2	4							
		3	4	13.1	14.4	9.0				
		4	4	16.4	17.3	5.2				
		5	4	15.0	19.8	24.2				
		6	4	15.0	16.8	10.7				
		7	4	16.5						
		8	4	13.5						
		9	3							
		10	3							
		11	3	10.1						
20	J. B. 58	1	5							
		2	4							
		3	4							
		4	4	12.4	13.6	8.9				
		5	4	14.5	16.5	12.0				
		6	4							
		7	4							
		8	4	19.5	22.4	12.8				
		9	4							
		10	0	17.0	19.7	13.6				
21	S. B. 40	1	4							
		2	4							
		3	3	18.2	20.5	11.2				
		4	3	14.0	15.9	11.9				
		5	3	13.8	15.7	12.0				
		6	3	12.7	14.9	14.8				
		7	3	13.3	14.5	8.3				
		8	3							
		9	3							
		10	3	14.8	16.7	11.3				
		11	3							
		12	3							
		13	3	16.4	18.1	9.3				
22	A. G. 30	1	6							
		2	3							
		3	3	22.3	24.4	8.9				
		4	3	20.0	22.2	10.0				
		5	3	18.5	20.3	8.8				
		6	3	17.8	19.1	6.7				
		7	3	16.5	17.7	6.7				
		8	3	16.8	18.3	9.1				
23	W. P. 59	1	3							
		2	3	3.9	5.0	22.0				
		3	3	5.2	7.7	32.5				
		4	3							
		5	3	4.4	6.5	32.3				
		6	3							
		7	3	4.5	7.4	39.1				
		8	3							
		9	3	4.4	8.6	48.8				
24	S. T. 65	1	2							
		2	4							
		3	4	20.8	23.3	10.7				
		4	3	20.3	23.8	10.5				
		5	3	16.2	19.7	17.7				
		6	3	16.9	19.8	14.6				
		7	3	17.4	19.6	11.2				
		8	3	19.6	21.3	7.9				
		9	3							
		10	0	9.6	10.8	11.1				
		11	0	5.1	5.8	12.0				

TABLE 2.—(*Continued.*)

			Sulfamerizine							
				Serum			Urine			
No.	Patient age (yrs.)	Day	Dose (gm.)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Daily excretion (gm.)
25	M. G. 45	1	3							
		2	3	8.9	12.4	28.2				
		3	3	9.6	13.4	28.3				
		4	3	6.8	9.8	30.6				
		5	3							
		6	3							
		7	3	8.8	11.5	23.4				
		8	3							
		9	3	11.4	16.1	29.9				
		10	3							
		11	3	9.5	12.4	23.4				
		12	3							
		13	3	11.5	16.2	29.8				
		14	3	11.0	13.5	18.5				
		15	3							
		16	3	10.5						
		17	1							
		18	0	6.0						
26	B. O. 68	1	3							
		2	4	19.1	22.0	13.1				
		3	3	25.9	28.9	10.3				
		4	3							
		5	3	12.7	14.8	14.1				
		6	3	14.4	16.5	12.7				
		7	3	14.8	16.0	7.5				
		8	3	18.1	19.4	6.7				
27	H. F. 35	1	3							
		2	4	10.7	15.0	28.6				
		3	4	10.3	15.4	33.0				
		4	0	10.4	14.2	26.8				
		5	0	2.5	2.5					
28	M. R. 40	1	2							
		2	2	8.7	10.1	13.8				
		3	2							
		4	2	11.0	12.6	12.7				
		5	2							
		6	2	9.0						
29	M. G. 51	1	2							
		2	2							
		3	2	13.3	14.5	8.2				
		4	2	12.0	13.0	7.7				
		5	2	10.4	11.4	8.7				
		6	2							
		7	2	9.8	10.9	10.1				
		8	2	8.9						
30	R. S. 28	1	2							
		2	6							
		3	6	22.8	24.6	7.3				
		4	25 (i.v.)	28.5	30.0	5.0				
				106.0*	113.4	6.5				
		5	0	79.4	85.2	6.7	439.0	606.3	27.5	2.42
		6	0	44.9	49.2	8.8	459.0	770.0	40.3	13.09
		7	0	19.7	21.3	7.4	357.5	516.3	30.7	4.12
		8	0	10.0	11.0	9.9	131.0	207.5	36.9	4.14
		9	0	4.4	4.4	..	26.3	49.4	26.5	1.97
		10	6	2.0	2.0	..	13.1	23.5	44.2	0.55
		11	8							
		12	5							
		13	0	26.1						
31	M. G. 17	1	2							
		2	6							
		3	6	21.1	24.9	10.5				
		4	6							
		5	15 (i.v.)	40.7	44.6	8.8				
				90.4*	97.2	7.0				
		6	0	73.2	78.1	6.3				
		7	0	38.5						
		8	0							
		9	6	8.0						
		10	6	24.0						
		11	6							
		12	6	25.6						
		13	6	35.0						
		14	6	35.0						
		15	6	39.0						
		16	6	25.5						

* One hour after intravenous infusion.

191.3 mg. per 100 cc. An average of 50.7% of the excreted drug was in the acetylated form with figures varying from 16.4% to 72.4%. Daily excretion of the drug varied from 26% to 82% of the ingested dose. One patient (No. 45) who received 25 gm. of sulfamerizine sodium intravenously excreted the amazingly high total of 13.09 gm. of the drug in the 2d 24-hour period after the infusion.

B. Distribution of Sulfamerizine in Various Body Fluids. I. *Cerebrospinal Fluid.* Twelve patients (Table 3) were divided into two groups in order to study the concentration of the drug in cerebrospinal fluid. The first group of 7 patients (Nos. 32 to 38, inclusive) were individuals without meningeal infection, to whom a single dose of the drug was given. Cerebrospinal fluid and blood specimens were then obtained at varying time intervals. Three hours after the oral administration of 3 gm. of sulfamerizine, the ratio of the cerebrospinal fluid level of free drug to that in serum was 0.09. After 6 hours the figure had risen to 0.1, and after 12 hours the cerebrospinal fluid concentration was 0.17 of that in serum. In 24 hours and after two 3 gm. doses the ratio was only slightly higher. The second group of cases included 5 persons (Nos. 19, 25, 39, 40, and 41) with meningeal infection under active treatment. Here the results were quite varied and the ratios ranged from 0.14 to 0.66.

Table 3.—Free Sulfamerizine Concentration in Various Body Fluids

Body fluid	No.	Patient	Hours after initial dose	No. of doses	Total dose (gm.)	Serum (mg. per 100 cc.)	Body fluid (mg. per 100 cc.)	Concentration ratio (body fluid/serum
Cerebrospinal fluid	32	F. M.	3	1	3	11.6	1.0	0.09
	33	P. L.	6	1	3	14.8	1.5	0.10
	34	V. A.	12	1	3	18.4	3.2	0.18
	35	H. A.	12	1	3	15.6	3.6	0.23
	36	P. L.	12	1	3	11.5	1.3	0.11
	37	F. Y.	12	1	3	14.9	3.2	0.22
	38	E. B.	24	2	6	22.5	4.4	0.20
	39	A. W.	18	2 (i.v.)	6	10.5	5.5	0.51
			36	4 (i.v.) 4 (p.o.)	17	10.0	3.3	0.33
	19	H. M.	48	8	9	16.1	3.7	0.23
	25	M. G.	264	16	19	8.8	1.2	0.14
	40	N. D.	39	7	8	8.9	1.6	0.17
	41	L. G.	15	2 (i.v.)	3	16.9	11.2	0.66
Pleural fluid	22	A. G.	480	35	37	10.6	10.5	0.99
	42	A. J.	12	1	3	5.9	2.4	0.41
	43	B. P.	12	1	3	8.4	1.7	0.20
Ascitic fluid	44	C. S.	12	1	3	4.4	2.3	0.52
	45	F. G.	12	1	3	6.4	3.6	0.56
	46	B. S.	12	1	3	7.0	3.0	0.43

II. *Pleural and Ascitic Fluid* (Table 3). Sulfamerizine seems to penetrate the pleural and peritoneal cavities readily. In 5 patients (Nos. 42, 43, 44, and 45) who received a single oral 3 gm. dose with simultaneous serum and body fluid specimens taken 12 hours later, from 0.2 to 0.56 of the serum concentration of sulfamerizine was found in pleural and ascitic fluid. In 1 patient (No. 22) after 37 gm. of the drug the serum and pleural fluid concentrations were almost equal.

III. *Erythrocytes and Blood Serum* (Table 4). Simultaneous determinations of sulfamerizine concentration in serum and whole blood were done at different times on 3 patients under continuous dosage. These results indicate a wide variation in red cell and serum concentration and are consistent with the work of others on sulfadiazine.[4]

TABLE 4.—DISTRIBUTION OF SULFAMERIZINE BETWEEN SERUM AND RED BLOOD CELLS

Sulfamerizine Concentration in Mg. per 100 Cc.

No.	Patient	Day of drug	Whole blood		Serum		Cells (calculated)		Packed cell vol. (%)
			Free	Total	Free	Total	Free	Total	
31	M. G.	18	21.1	23.8	29.5	32.6	7.4	9.5	38
		19	18.1	22.2	26.4	29.6	4.5	10.0	
47	J. M.	2	13.2	..	17.0	..	8.4	..	44
		3	10.5	13.8	17.2	19.9	2.0	6.1	
48	J. H.	3	4.9	6.3	6.0	10.9	2.8	?	35

Discussion. Comparison of this work on sulfamerizine with studies by Reinhold *et al.*[5] on sulfadiazine (making allowances for differences between whole blood and serum concentrations) indicates that sulfa-

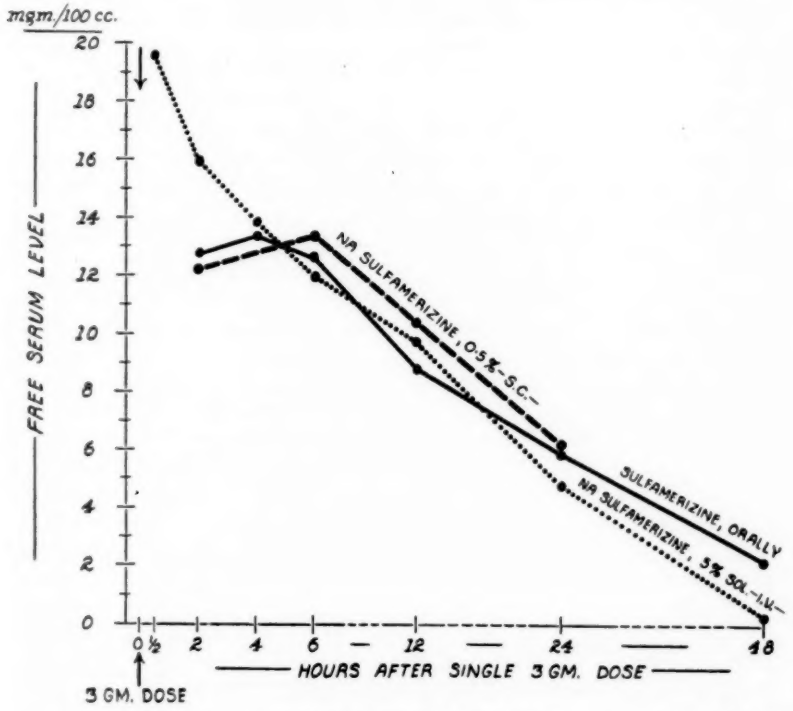

FIG. 1.—Average serum concentration of free sulfamerizine following a single 3 gm. dose by various routes.

merizine is more rapidly and probably more completely absorbed from the gastro-intestinal tract than sulfadiazine. Furthermore, experience with continued administration has shown that smaller doses are

required to attain and maintain a given blood level with sulfamerizine than with sulfadiazine.

Subcutaneous infusion of sulfamerizine sodium results in serum levels closely approximating those obtained when the same dose of sulfamerizine is administered by mouth (Fig. 1). Intravenous administration of sulfamerizine sodium gave high serum concentrations of the drug shortly after injection. However, the serum concentrations and rate of disappearance of sulfamerizine are about the same after the first 4 hours following a given dose, regardless of the route of administration of the drug, except for the fact that sulfamerizine is not absorbed rectally (Fig. 1).

Sulfamerizine penetrates readily into the body fluids studied. However, in view of the experience with sulfathiazole this should probably not be given any great weight in predicting the therapeutic effectiveness of the drug.

The rate of urinary excretion of both free and acetylsulfamerizine relative to dose is about the same as that found with sulfadiazine.[5] In view of the greater urinary solubility of both the free and acetylated forms of sulfamerizine,[8] the incidence of urinary complications may be less than with sulfadiazine.

Summary. 1. The behavior of sulfamerizine has been investigated in 28 convalescent patients serving as controls and in 20 patients suffering from acute bacterial infections.

2. The data presented indicate that after a single 3 gm. oral dose of sulfamerizine higher blood serum levels are attained more rapidly and sustained longer than after similar amounts of sulfadiazine.

3. Desired serum concentrations can be obtained by giving sulfamerizine sodium subcutaneously or intravenously.

4. Sulfamerizine is readily distributed through body fluids and enters the red cell in varying concentrations.

5. Sulfamerizine is slowly excreted in the urine in amounts roughly comparable to sulfadiazine.

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CLOT RETRACTION TIME IN THROMBOPHLEBITIS AND PULMONARY EMBOLISM

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The properties of blood in thrombophlebitis, phlebothrombosis and pulmonary embolism have been studied by several investigators, notably Lampert,[5] during the last two decades. Valuable contributions to our knowledge of the etiology of these conditions have been made. It is quite generally accepted that the blood platelets and plasma fibrinogen are elevated in most of these cases, particularly when pulmonary embolism has occurred. Barker, Nygaard, Walters and Priestley[1] have demonstrated statistically that anemia is a definite predisposing factor in pulmonary embolism. These 3 hemic factors, blood platelets, plasma fibrinogen and anemia, working together result in a rapid clot retraction time.

The clot retraction time has been observed routinely by hematologists in the study of hemorrhagic diseases. In thrombocytopenia, clot retraction is absent or greatly prolonged. The platelets are considered to be essential for the development of clot retraction because of this phenomena. Hemorrhage may occur with thrombocytopenia even though the coagulation time is normal. On the other hand, thrombosis is also usually associated with a normal coagulation time. This apparent disparity between blood coagulation in a glass tube and within the body has been a problem of great physiologic importance. If a prolonged clot retraction time rather than a prolonged coagulation time is an index of hemorrhagic tendency in thrombocytopenia, it is possible that states characterized by hypercoaguability *in vivo* with normal coagulation times *in vitro* may be associated with a very short clot retraction time.

There may be considerable variation in the clot retraction time in the non-hemorrhagic diseases. Katrakis[4] demonstrated that in a variety of surgical conditions, more serum was formed during the early 15-minute periods after coagulation in those cases exhibiting cachexia or infection. Lampert[5] suggested that these observations may explain why some surgical patients have pulmonary embolism. The early formation of serum is the result of rapid and strong clot retraction, and if a thrombus has recently formed in such a patient, it is possible that pulmonary embolism is likely to occur because of the great ease with which the thrombus detaches itself from the vessel wall.

Figure 1 demonstrates that short clot retraction times do occur in association with pulmonary embolism. The clot retraction time was determined by the method of Hirschboeck and Coffey.[3] In 9 out of 10 cases of pulmonary embolism, the clot retraction time was less than

10 minutes. In the 10th case, the embolism occurred in a decompensated cardiac patient convalescing from a pelvic operation. The normal clot retraction time varied between 25 and 35 minutes.

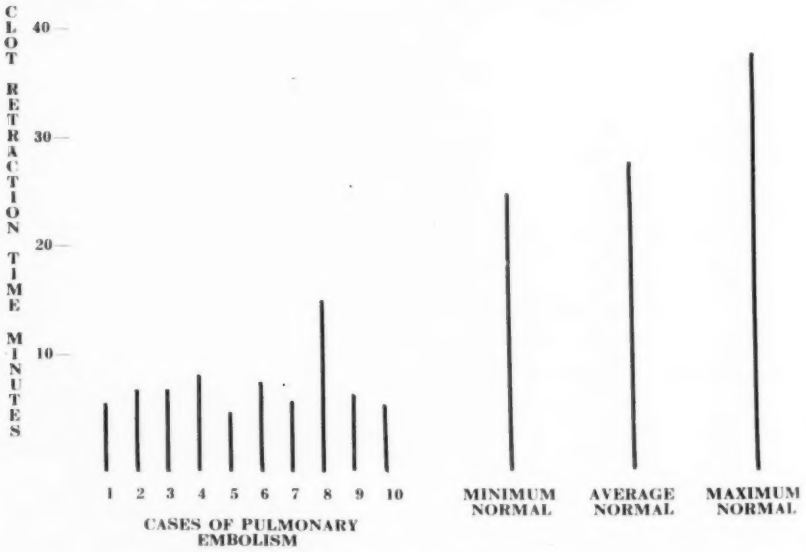

FIG. 1.—Clot retraction time in pulmonary embolism.

The phenomenon of clot retraction has been likened to syneresis. Most gels of all types will, after standing for a period of several days, retract slightly from the walls of their containers. The degree of retraction is slight and does not equal that produced by a blood coagulum. The structure of the true gels and a blood coagulum are entirely different. The blood coagulum is a tangled meshwork of adherent strands of fibrin, whereas a true gel has microscopically an amorphous structure. Although coagulated blood may appear grossly similar to a gel, it is microscopically quite different. Attempts to explain clot retraction in terms of syneresis are therefore not entirely valid.

Inasmuch as the blood platelets are involved in the phenomenon of clot retraction, variations in their number can be expected to influence the clot retraction time. One would anticipate a short clot retraction time with thrombocytosis and a prolonged clot retraction time with thrombocytopenia. This is evidently the case when the number of blood platelets is well above or below the average levels. In a case of chronic myelogenous leukemia with a platelet count of 1,400,000, the clot retraction time was $2\frac{1}{2}$ minutes, while in thrombocytopenia, with platelet counts of 15,000, there may be no clot retraction. These great extremes in platelet counts occur only in the so-called blood dyscrasias and are never encountered in the ordinary case of pulmonary embolism. Although definite elevations in platelets occur postoperatively and during acute infections, they are to an extent capable of only slightly

affecting the clot retraction time. Anemia and a high fibrin content are more important in the speed and degree of clot retraction in these conditions.

The sedimentation rate of erythrocytes is, for the most part, determined by the fibrinogen levels of the blood plasma.[2] When the fibrinogen increases, the sedimentation rate is more rapid. Therefore, blood with a rapid sedimentation rate contains more fibrin when in the coagulated state. It is this increase in the fibrin matrix of the clot which is probably responsible for its more rapid and more forceful retraction.

TABLE 1.—SEDIMENTATION RATE AND ERYTHROCYTE CONCENTRATION IN 126 CLOT RETRACTION TIME DETERMINATIONS

Clot retraction	R.B.C. in hematocrit (%)	Uncorrected sed. rate	Corrected sed. rate	No. of cases
6–10 min.	39.9	40.4	28.4	16
11–15 "	37.4	35.4	24.5	30
16–20 "	45.1	27.6	24.1	25
21–25 "	44.4	22.7	19.9	21
26 min. and beyond	49.0	15.4	16.8	34

Anemia is generally regarded as a contributing factor in the development of pulmonary embolism. With anemia, the erythrocyte concentration, as measured by the hematocrit, is below the normal of 45%. Erythrocytes play an entirely passive rôle in the process of coagulation. After the clot is formed, they, together with the serum, fill up the spaces between the tangled network of fibrin. When retraction takes place, the fibrin strands come in closer relationship to each other and shrink down on the entrapped erythrocytes, and at the same time force the serum out of the clot. In anemia the plasma portion of the blood with its dissolved fibrinogen is proportionally much greater than the erythrocyte percentage. Coagula of anemic blood contains more fibrin, more serum and less erythrocytes than normal blood. When these clots retract, the amount of inert erythrocyte bulk filling the spaces between the mesh is less and the amount of fibrin is more than normal. There is then a more likely probability of rapid and powerful clot retraction. In erythremia the reverse is the case, and here, as might be expected, retraction is very slow or does not take place at all.

This relationship of sedimentation rate and erythrocyte concentration, as measured by the Wintrobe and Landsberg[6] technique to clot retraction time, is demonstrated in Figure 1.

Heparin as well as other anticoagulants (sodium citrate, sodium fluoride), when used in amounts not large enough to inhibit completely coagulation but merely to delay it, will prolong the clot retraction time. The effect is also produced with heparin when it is given intravenously. Small doses of 100 mg. given at daily intervals will prolong the clot retraction time into the normal range. The mechanism of action of these anticoagulants on clot retraction is not known, but it apparently lies in their stabilizing effect on the blood platelets, reducing their physiologic activity with a resultant thrombocytopenic-like effect on the blood.

Summary. Hemodynamic factors, local tissue and vascular trauma are of great importance as etiologic factors in the development of phlebothrombosis and pulmonary embolism; but anemia and elevation of blood fibrinogen and platelet levels are also of major importance and these working together result in a rapid and powerful clot retraction. The strength and rapidity of clot retraction is perhaps responsible for the loosening of thrombi from vessel walls and explains the coincidence of short clot retraction times with the occurrence of pulmonary embolism. Small amounts of heparin greatly prolong the clot retraction time; the prophylactic use of heparin in patients with short clot retraction times should reduce the incidence of pulmonary embolism.

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A CASE OF EXTREME HYPOTENSION FOLLOWING ACUTE ARSENIC POISONING WITH ADEQUATE BLOOD SUPPLY TO THE TISSUES

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The effect of prolonged periods of excessively low arterial pressure on animals and man has been a subject of interest for many years. Recrudescence of investigation on this subject in its relationship to shock has made it seem desirable to publish observations made on a patient recently studied in the Lilly Clinic.

This patient was unusual in that the arterial pressure was very low for a period of about 18 hours, yet he seemed to suffer no ill effects from it, we believe, because the peripheral tissues received adequate amounts of perfused blood, despite the low head of pressure. In this respect the clinical picture differs fundamentally from shock in which the head of pressure is low but peripheral perfusion is inadequate.

Clinical Description. At 9 P.M. a despondent 39-year-old white male took 15 gm. of arsenic trioxide. Within 10 minutes, he began vomiting and retching and had bloody diarrhea. At 11 P.M. he walked into the receiving ward of the Indianapolis City Hospital. His stomach was washed with 2000 cc. of 1:1000 potassium permanganate solution and 1000 cc. of normal saline was started as an intravenous infusion. His arterial blood pressure was 65/35 mm. Hg, pulse rate 94, temperature 98.8° F. One liter of 5% dextrose in distilled water

was added to the infusion at 2 A.M. Mental confusion was noted during the night. At 9.15 A.M. his arterial blood pressure was 45/0 mm. Hg; pulse rate 98. At this time, he felt well and was able to walk and converse. He was a little cloudy mentally, but this confusion was due to a psychosis that later became evident. At 9.30 A.M. he voided in bed. At 10.30 A.M. he was transferred to the Lilly Clinic. He sat up on the cart, walked from the cart to bed with no assistance. His temperature was 97.8, pulse rate 114, respiratory rate 26 per minute and arterial blood pressure was 38 mm. Hg.

The physical findings were hypotension, generalized flushing of skin, absent pupillary light reflex with accommodation reflex present, distant first heart sound and barely audible second sound. Pulse rate was 114. Blood Kline and Kahn reactions were 4+. Red blood cell count was 5.27 million; white blood cell count 21,400; hemoglobin 90.3%; hematocrit 36.0%. Total plasma proteins were 7.2 gm./100 cc. Blood urea nitrogen 37.6 mg. per 100 cc.; blood chloride 584 mg. per 100 cc.; blood calcium 9.1 mg. per 100 cc.; blood phosphorus 4.9 mg. per 100 cc.; venous blood CO_2 combining power was 30.8 vol. per 100 cc.; arterial CO_2 combining power was 29.3 vol. per 100 cc.

Skin temperatures were 33.75° C. on left arm; 33.0° C. on right arm; 36.0° C. on left abdomen; 35.5° C. on right abdomen; 33.25° C. on left leg, and 33.5° C. on right leg.

The ECG was interpreted as being normal and ballistocardiographic tracings were normal with pulse rate of 112; stroke volume per 1.73 sq. meters body surface was 82 cc. (normal 70 cc.); and cardiac output 5.3 liters per 1.73 sq. meters/minute (normal 2.8 liters). Peripheral resistance (R = 3 Pm/CO) was 17 (normal 100).

Peripheral pressor substance as measured by perfusing plasma through an isolated rabbit's ear and ascertaining the amount of vasoconstriction[1] was comparable to normotensive person's during the period when the patient's arterial blood pressure was 48 mm. Hg mean pressure and later 60 (76/44 mm. Hg). Renin-activator as measured by the activation of human renin in a pithed cat was present in amounts comparable to a normotensive.

With so many normal findings in a patient apparently little disabled by the poison, the accuracy of the auscultatory measurement of arterial blood pressure was questioned. A 19-gauge needle was inserted into the femoral artery and connected to a mercury manometer. Mean arterial blood pressure was 30 mm. Hg. Intravenous angiotonin (4.5 cc.) given over 5 minutes time gave a rise in mean pressure to 98 mm. Hg with no change in pulse rate. Intravenous injection of 3 cc. of 1:10,000 adrenalin given over a 2-minute period gave a rise in mean pressure to 136 mm. Hg and tachycardia of 140. At the completion of these studies, it was 12.30 P.M., or 15½ hours since ingestion of arsenic. The patient had become anuric. As noted above, he voided in bed at 9.30 A.M. There is no way of knowing how long this urine had been in his bladder.

During the morning he was coöperative but talked with slurred speech of grandiose matters. He ate an egg sandwich and drank 2 glasses of milk. Immediately following this, he had a chill lasting 20 minutes. His temperature rose to 103° F. His arterial pressure varied from levels which were imperceptible by the auscultatory method to 40 mm. Hg systolic, levels too low to filter urine through the glomeruli of the kidneys. Following the chill, he became more irrational and quite violent, necessitating restraint. At 4.45 P.M. an infusion of 1000 cc. of normal saline was started. Three hours later he was quiet and coöperative. He had a bloody stool, the first time since admission. He was still anuric with systolic blood pressure of 40 mm. Hg. At this time an infusion of plasma was started simultaneously with an infusion of 500 cc. of normal saline containing 50 cc. of angiotonin. The blood pressure was maintained at 70 to 100 mm. Hg systolic by regulating the drop rate of angiotonin. On one occasion the inflow of angiotonin was increased to elevate the arterial blood pressure to 130/80 mm. Hg. At this pressure level, he talked in a wild manner, struggled and fought the attendants. By decreasing the infusion rate, blood pressure was reduced to 70/40 mm. Hg. He became calm and quiet but was still grandiose.

At 10.45 P.M., 25 hours after taking arsenic, angiotonin was discontinued. By infusing normal saline rapidly, arterial blood pressure was maintained at 70 to 90 mm. Hg systolic and 30 to 40 mm. Hg diastolic until midnight. At this time, 15 cc. of urine were obtained with a catheter. The specific gravity was 1.022; it was loaded with granular (80%) and hyaline casts (20%), there were 20 to 30 white blood cells and 5 to 10 red blood cells per high-powered field. Curiously, there was no protein present. At 1 A.M. arterial blood pressure had fallen to 64/30 mm. Hg. Ephedrine, gr. $\frac{3}{8}$, was given subcutaneously. This was followed by a rise in pressure to 100/40 mm. Hg. He again became violent, grandiose and abusive. Sodium phenobarbital administered subcutaneously induced sleep for the remainder of the night. At 8 A.M. 40 cc. of urine was obtained by catheter. During the morning of the second day 2000 cc. of 10% glucose in water were given intravenously. Two-and-a-half hours later he voided 600 cc. of urine. Specific gravity was 1.004; it was free of casts, white blood cells and protein. Dr. R. N. Harger found 1 mg.+ of arsenic per liter of urine. Blood urea nitrogen was 59.5 mg. per 100 cc.

Aside from mental confusion and occasional attacks of violence, he was apparently quite well. Arterial pressure maintained itself between 100 and 120 mm. Hg systolic and 40 to 60 mm. Hg diastolic. Cardiac output was 4.53 liters/1.73 sq. meters/min. (normal 2.8 liters) and stroke volume was 77 cc. (normal 70 cc.). Red blood cell count was 4.35 million; peripheral resistance was 53 (normal 100); white blood cell count 15,500; hemoglobin 86.1%; and hematocrit 36%. Blood urea nitrogen had fallen to 41 mg. per 100 cc. and total plasma protein to 4.66 gm./100 cc. on the 3d day of illness. Dr. A. C. Corcoran of this laboratory measured renal blood flow by diodrast clearance on the 4th day after ingestion of the poison and found it to be 669 cc. per min. Inulin clearance was 33.9 cc. per min.; filtration fraction, 0.08.

With blood pressure at normal levels, and patient voiding, it was possible to investigate more freely the notion that the patient had central nervous system syphilis as well as arsenic poisoning. The pupils showed the Argyll-Robertson phenomenon, speech was slurred, delusions of grandeur were present, and the blood Kline and Kahn reactions were positive.

The patient's mother furnished the history later relative to his mental changes. She stated that his mind had become more and more childhish over the past 2 years. He often made claims of wealth and prestige that were utterly false. The cerebrospinal fluid pressure was 220 mm. of water. The fluid gave a 4+ Wassermann reaction; 2+ globulin reaction; gold curve was 555443110; cell count 9 lymphocytes. The diagnosis of general paresis was confirmed. From this time on, his course was that of fulminating paresis with increasing stupor, abdominal distention, hyperpyrexia and death, 10 days after ingestion of the arsenic trioxide.

Postmortem examination of the brain confirmed the diagnosis of general paresis. There were no gross lesions in either the thorax or abdomen. Sections taken from the liver and kidney examined by the Coroner proved to be normal.

Discussion. The observations on this patient suggest that arterial blood pressure may be profoundly reduced and remain so over long periods of time without causing pathologic changes. Despite the fact, that the mean arterial pressure, measured by femoral arterial puncture, was only 30 mm. Hg, he was able to walk and coöperate satisfactorily. Indeed, when the blood pressure was raised to normal levels by plasma and angiotonin he tended to become disoriented. It is of especial interest that at no time was his skin pale or cold as in the state of shock. On the contrary, it was warm and at times flushed. We assume that these signs signified adequate perfusion of the tissues with blood.

The hemodynamic changes associated with the low arterial pressure were interesting. Cardiac output was nearly doubled, due to increased

stroke volume and rate, while peripheral resistance was only about one-fifth of normal; in short, conditions making for excellent perfusion of the tissues.

The renal vasopressor system was apparently not called into play by the reduced pressure, as no increase above normal in either the peripheral vasoconstrictor substance or renin-activator was found. Peripheral vasoconstrictor substance (P.V.C.S.) has been found by Page[2] in the plasma of hypertensive patients and animals and in normotensive animals after injection of renin. Its chemical nature is not known. It is determined by perfusing small samples of the unknown plasma through an isolated rabbit's ear perfused with blood. When plasma containing or forming peripheral vasoconstrictor substance (P.V.C.S.) is injected, immediate constriction occurs in the vessels of the ear.

Renin-activator was determined because several years ago it was shown[3] that in hypertensive patients the amount of it is increased. Presumably this increase is a response on the part of the liver to the increased need for this substance, for it has been shown that the liver is the source of renin-activator.[4]

The response to intravenously injected angiotonin was excellent and it was possible to keep the arterial pressure elevated by simultaneous injection of angiotonin and plasma. The maintenance of pressure was evidently largely due to the angiotonin because when it was temporarily discontinued, despite continued administration of plasma, the arterial pressure fell. Since the heart rate did not rise during the angiotonin administration it seems reasonable to suppose that the elevation in pressure was due to increased arteriolar resistance and augmentation of the force of the heart beat.[5] In fact, after the blood pressure had been restored to nearly normal, the peripheral resistance rose from 17 to 53.

Since the blood pressure was well below the level necessary for glomerular filtration, it is not surprising that there was a period of anuria. This was followed by partial recovery of renal function and blood flow by the 4th day after poisoning.

This clinical experiment suggests to us that arterial pressure may be profoundly reduced without serious damage to tissues other than the kidneys if tissue perfusion is still adequate.

We have searched the literature for similar studies on the effect of arsenic trioxide and other arsenic compounds on arterial pressure. A few suggest that these substances elevate blood pressure and a few that they lower it. None carry conviction.

It is interesting that the patient suffered from general paresis and that many of his mental symptoms were expressions of that disease. Administration of large amounts of inorganic arsenic appear to have reactivated the disease, a not uncommon occurrence seen in ill-advised therapeutic attempts with organic arsenic compounds.

Summary and Conclusions. A paretic was studied who took 15 gm. of arsenic trioxide with suicidal intent. We were amazed to find that he was able to walk and coöperate despite the fact that mean intra-

arterial blood pressure was only 30 mm. Hg. The other striking feature was that tissue perfusion seemed excellent; the only function appearing to suffer being the ability of the kidneys to secrete urine.

The patient was able to maintain adequate perfusion of the tissue by doubling the output of the heart and greatly reducing peripheral resistance. The renal vasopressor system did not respond to the hypotensive stimulus possibly because pulse-pressure was not reduced.

Infusion of angiotonin and plasma restored the arterial pressure to normal after a period of about 18 hours severe reduction.

The patient seemed to have few ill-effects from this episode except that, associated with it, reactivations of general paresis occurred, from which he had previously suffered, leading to his death.

This clinical experiment suggests to us that reduction in arterial pressure need not lead to serious consequences if the perfusion of the tissues remains adequate. In this respect the clinical picture was the reverse of shock in which both arterial pressure and tissue perfusion are severely reduced. The importance of obtaining better tissue perfusion in shock rather than elevating arterial pressure—the converse of the hemodynamic state in our patient—is suggested by these observations.

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THERAPEUTICS

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ESTROGENS AND ANDROGENS

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Estrogens. *Compounds.* Following the clinical availability of pure potent estrogens there were published numerous enthusiastic reports on the successful treatment of a wide variety of endocrine and non-endocrine conditions. There has been sufficient time now, however, for the resulting confusion to have cleared considerably, and the actual worth of estrogens to be evaluated on a relatively sound basis. In the past few years, estrogen therapy has been firmly established on a scientific rationale and additional experimentation has furthered our knowledge of this subject. Some of the more recent developments are centered on improving the known estrogens for therapeutic purposes, as well as the introduction of entirely new compounds. The two most commonly used natural estrogens, estrone and estradiol, have been modified in several ways so as to render them more efficient. The methods used in modifying these estrogens rest upon the fact that they are rather readily destroyed when introduced into the animal body. It has been conclusively demonstrated that they are destroyed by the liver, either by conjugation with glucuronic acid or through alterations to metabolic by-products and excreted in such forms.

Estradiol can be combined with certain common inert substances so as to lessen the destruction by the body. Thus, the compounds estradiol benzoate and dipropionate are more efficient than the free compound, because of the fact that these compounds have a decreased rate of absorption at the site of injection so that the estrogen enters the blood stream at a slower rate and over a more prolonged period of time. This mechanism resembles that of the ovaries which also elaborate estrogen in relatively small amounts but at a slow rate. Estrone cannot be combined with inert substances with advantage and therefore suffers in this respect. Another compound of estradiol, recently introduced, is ethinyl estradiol which is apparently more potent by mouth than any other compound of

estradiol. This preparation was designed to meet the increasing demand for more convenient estrogen therapy which is made available through oral administration. In this respect, one of the newest available natural estrogens is estrone sulfate. This substance occurs in the urine of pregnant mares together with sulfates of the other naturally occurring estrogens. From laboratory experiments, it is claimed that this compound is 3 times as potent orally as free estrone. In human experiments it has been proven to be potent by mouth in dosages somewhat smaller than one would expect by application of laboratory data.

Probably the most efficient means of supplying estrogens for clinical purposes, where long-continued applications are desired, is with the use of crystals of estrogens or pellets made from crystals, which are introduced by subcutaneous implantations. Since the estrogens are steroids and water-insoluble, these implants dissolve slowly in the tissue fluids at the site of implantation, and therefore are absorbed very slowly into the blood stream. Such implants will produce an estrogenic effect over long periods of time without additional therapy. Bennett and Te Linde[8] maintained that of all the methods of estrogenic therapy they have used, the one using the implantation of crystalline estrone is the most effective method yet devised for combating the menopausal syndrome, where long-continued effects are desired. These authors did not use any other natural estrogens in pellet form. It has been reported, however, that pellets may fail to be absorbed after some time because of the connective tissue scarring about the pellets. Another disadvantage to pellet implantations is the inconvenience of this type of therapy, although the technique used formerly by incision has been supplanted by the use of large bore needles with a trocar for inserting the pellets. Physicians seem, however, loathe to use pellet implants in general practice. For this purpose, therefore, a method has been devised which utilizes the principle of crystal implantation, but by simple intramuscular injections with an ordinary syringe. Thus, estrone crystals have been suspended in aqueous solution.[24] This material is drawn into an ordinary syringe and injected intramuscularly. The aqueous medium is absorbed rapidly leaving a small deposit of crystals. While such a technique does not, of course, parallel the results following the deposit of large pellets or a large amount of crystals it appears to be the most satisfactory method of administrating estrone with an ordinary syringe. In addition, the use of an aqueous suspension of crystals does not introduce the possibility of sensitivity reactions to the oil vehicle common to most injectable estrogens.

Great strides have been made with the introduction of synthetic estrogens. Not only has this resulted in the availability of estrogens at economic cost, but has opened up new fields for estrogen therapy because of the ease of administering large dosages of estrogens. These synthetic estrogens may be and most commonly are, administered by mouth. Most attention has been given to the first highly potent synthetic estrogen developed, namely diethylstilbestrol. This estrogen prepared from nonbiologic materials is capable of producing most of the physiologic effects of natural estrogens. There is some slight difference in the metabolic and pharmacologic reactions of this material from that of the natural estrogens. There was considerable resistance in this country to the acceptance of this substance because of the early reports regarding its possible toxicity since experimental work had demonstrated that this compound might impair the function of the liver and bone marrow and cause certain unpleasant symptoms following its administration in humans.

Both the Food and Drug Administration and the Council on Pharmacy and Chemistry have accepted this compound on the basis of clinical and laboratory reports which claim that this compound is no more toxic than natural estrogens in equivalent dosages.[54] Since its official acceptance, only two reports have appeared which would indicate the possibility of harm arising from its use and these reports concern 2 cases where allergic response to diethylstilbestrol were encountered. The origin of nausea and other disagreeable symptoms which are relatively frequent complications of diethylstilbestrol therapy have been shown rather satisfactorily to be on a physiologic basis of non-specific nature rather than from any pathologic lesion.[22] Thus, Freed and associates have maintained that nausea following diethylstilbestrol administration is a result of its rapid absorption into the blood stream giving rise to symptoms which could be explained on the basis of water retention in the tissues. Thus, headache is produced by cerebral edema, nausea from edema of the gut, etc.[25] When the absorption of diethylstilbestrol is delayed through combining it with a fatty acid, toxic symptoms are reduced. Greene and Ross have demonstrated that diethylstilbestrol dipropionate gives rise to disagreeable symptoms less than half as frequently as the free compound.[33] In this respect, Freed and associates have shown that diethylstilbestrol dipalmitate gives rise to little or no disagreeable symptoms and has a remarkably prolonged beneficial action in the menopause because of its unusually slow absorption at the site of injection.

Diethylstilbestrol has also been used in the form of pellets, but this does not appear to be satisfactory, inasmuch as oral therapy is more readily controlled and quite convenient.[47] Considerable experimentation has been made with the monomethyl ether of diethylstilbestrol or methylstilbestrol. There is some controversy as to its advantages over the free compound.[13,19] Dihydrodiethystilbestrol or hexestrol has also been used. There is some evidence that this is somewhat less toxic than the parent compound, although it is reported in this country to be from one-fifth to one-tenth as active. An entirely different synthetic estrogen has been recently made available commercially. This compound is called Octofollin (118B) and has no relationship chemically to diethylstilbestrol or the natural estrogens. It has the formula 2, 4-di (para-hydroxyphenyl)-3-ethyl hexane. It has been shown to be a potent estrogen by laboratory and clinical experimentations.[12,26] Robson and Schönberg have introduced another new estrogen which has a prolonged action when given orally.[56] It is a derivative of triphenylethylene with the formula, alpha, alpha-di-(para-ethoxyphenyl) beta-phenyl bromo-ethylene. This compound is called for convenience, D.B.E. This substance is the only estrogen known that has a prolonged action when given by mouth. It is thought to be stored in the body and released slowly to produce its prolonged effect. There are as yet no clinical reports on this substance. Still another estrogen of promise, which has been shown to be effective in relatively small doses, is 8-di-p-hydroxy-phenyl-$\triangle$ B8 hexadiene or more conviently "dinestrol." Barnes has shown it to be about 10 times as potent as diethylstilbestrol in the suppression of lactation when administered by mouth.[6]

Therapy. Following the initial deluge of reports on the use of estrogens for a wide variety of conditions, there has developed a far more sound point of view on the indications and contraindications for estrogen therapy. Most authorities, including the Council on Pharmacy and Chemistry, have recognized that estrogens are worthwhile in conditions such as the

menopause and its complications, senile vaginitis, kraurosis, and gonorrheal vaginitis of infancy. With the introduction of higher dosage forms of estrogens following the development of the synethetics, the Council included in its list of indications the suppression of lactation and prevention of painful breast engorgement. A number of other conditions have been subjected to therapeutic trials with estrogens with promising results, although definite conclusions cannot be drawn as to the ultimate value of such therapy. These conditions are functional uterine bleeding, dysmenorrhea and a variety of non-endocrine disorders.

In the treatment of menopausal symptoms, estrogen therapy is on a far more satisfactory basis than before. The synthetic estrogens have offered inexpensive products with a wide flexibility of range for administration. The oral administration of such estrogens relieves the patient of frequent visits to the physician for hypodermic injections. It is considered advisable to administer such estrogens cyclically with frequent rest periods. The commonly used synthetic diethylstilbestrol has an average dose of 0.5 to 1 mg. daily. The chief disadvantage of this compound is the development of unpleasant symptoms in a significant percentage of patients. While no actual tissue damage is produced the untoward symptoms may cause many patients to refuse to undergo such therapy. It is known that the incidence of the disagreeable symptoms, chiefly nausea, dizziness and headache, is in proportion to the size of the dose. Therefore, if therapy is started with small amounts, some patients may be spared the development of these reactions. Enteric coating, bile salts, alkali and various other procedures claimed to eliminate the toxicity are of doubtful value in view of the fact that these symptoms are of systemic, not local, origin.

The use of other compounds of stilbestrol has been tried to a considerable extent. Hexestrol is effective in doses which are considerably greater than those of diethylstilbestrol. This, however, should cause no objection because the cost of the active material is practically insignificant in therapeutic doses. Freed and associates found that 2.5 to 5 mg. daily of hexestrol is the average therapeutic dose.[26,27] Bieren and Compton[9] found that 10 mg. daily appears to be a satisfactory dose. The incidence of toxicity is reported to be somewhat less than for diethylstilbestrol. Methylstilbestrol has also proven to be an effective estrogen. There is some disagreement, however, as to the actual potency of this material. Geschickter and Byrnes[29] maintain that 2 mg. daily is an effective dose which is also equivalent to that of diethylstilbestrol. Abarbanel[1] maintains that the monomethylether is one-fifth as active as the parent compound.

Oral estrogens other than the stilbenes have been developed which may prove satisfactory. Octofollin is approximately one-half as active as diethylstilbestrol, according to Freed and associates.[27] In therapeutic doses there are relatively few toxic reactions. These results have not been confirmed as yet in published articles while Taylor and Thompson[66] have failed to confirm these results. As yet this compound has only been used in the treatment of the menopause. Menopausal patients have been encountered where bleeding appeared following octofollin therapy and the author has been able to induce bleeding in a few cases of amenorrhea.

The natural oral estrogens used in the newer treatment of the menopause are ethinyl estradiol and estrone sulfate. While there is considerable evidence that the former is active in doses of 0.5 to 1 mg. daily, there is evidence that at this dosage level the material may be toxic and therefore

possess no advantage over the stilbenes.[58] Estrone sulfate has been available on the market too recently for a complete evaluation. Nevertheless, the early evidence points to the fact that in the dosage of 1 mg. daily, most patients will obtain satisfactory relief from their symptoms.[27] It has also been noted that patients may prefer this estrogen to some of the stilbene compounds because it gives a greater sense of general relief. It has been suggested that while diethylstilbestrol may eliminate some of the symptoms of menopause, such as hot flashes, they fail to give this feeling of well-being. It is possible that it often induces a low grade toxic reaction which is insufficient to be considered definitely a disagreeable symptom such as nausea or headache, but is interpreted by the patient as a failure to feel well.

The use of pellet implants is a most efficient form of therapy, since the administration of 25 to 50 mg. of an estrogen in a pellet will afford relief for a number of months without additional therapy. In fact, Salmon and associates[58] maintain that the implantation of estrogen crystals before castration will prevent the appearance of symptoms for many months, and as long as 2 years in a number of patients. Bennett and Te Linde[8] recommend pellet implants of estrone as the most effective method devised for combating the menopausal syndrome. However, pellets are not yet available on the market. There is a possibility that some of the estrogens may be improved further so that even pellets may not be considered to possess advantages. In this regard, Freed and associates have introduced diethylstilbestrol dipalmitate.[26] This combination of estrogen with a relative high fatty acid was injected in dosages containing 5 mg. of the active compound 3 times at weekly intervals. The period of relief from symptoms following cessation of therapy averaged 8 to 9 weeks. In some unpublished work the author has found that one injection of a 5 mg. dose in about 200 instances produced relief, on the average, for 5 weeks. It is obvious that compounds developed along these lines with, for instance, even higher fatty acid esters may be even more effective, or that an injection of 10 or 15 mg. will produce results equivalent to that of pellets.

The ability of estrogens to suppress lactation has been established rather satisfactorily following the introduction of the synthetic estrogens. Diethylstilbestrol, chiefly, has been used for this purpose.[1,15,64] The natural estrogens appear to be equally effective, but have the disadvantage of being costly. Inasmuch as lactating women are tolerant to diethylstilbestrol compounds, there appears to be no drawback to the use of these synthetic compounds in this condition. It has been adequately proven that the administration of these estrogens is more effective in the early postpartum period, and that the estrogens have little effect on lactation where nursing is maintained.[1] Dinestrol has been shown to be 10 times as potent as diethylstilbestrol in suppressing lactation.[6]

Estrogens have been demonstrated to be effective in relieving the pain of patients with dysmenorrhea. The administration of estrogen for this purpose depends, according to some workers, upon suppressing ovulation.[65] The material is injected or administered orally in the first 2 weeks of menstrual cycle, thereby suppressing the gonadotropic hormones of the anterior pituitary so that the subsequent menstrual period becomes anovulatory preventing the pain which has been claimed to be dependent upon the presence of the corpus luteum. Hirst and associates[39] have obtained satisfactory results with this therapy but do not agree that relief is due to suppression of ovulation.

One of the more promising features of estrogen therapy recently developed is the treatment of uterine bleeding. Karnaky[41] demonstrated that estrogens in sufficiently high dosage will stop practically any type of uterine bleeding. The dosages are rather high, as much as 25 mg. of diethylstilbestrol daily. He maintains that the bleeding from fibroids, polyps, tubal pregnancy and functional conditions may be effectively combated in this manner. He has also demonstrated that the injection of estrogens directly into the cervix will bring prompt suppression of bleeding. Confirmation of this work has not been published except for the work reported by Palmer,[50] and Cuyler and associates,[16] who have demonstrated that diethylstilbestrol is effective in suppressing functional uterine bleeding. It appears that the functional bleeding of meno-metrorrhagia in the premenopausal period may be controlled by relatively small dosages of estrogens. In younger women, the excessive bleeding of menorrhagia, apparently requires much larger doses of estrogens. The biphasic nature of the therapy of functional bleeding is based on two factors. In the functional bleeding during the active reproductive life it is necessary to suppress the anterior pituitary in order to reduce the activity of the ovary. This is brought about with large doses of estrogens. Certain types of bleeding, especially that found in the premenopause, may be due to a diminished ovarian secretion of estrogenic hormone resulting in a lowered blood estrogen level, in the neighborhood of the bleeding threshold of the uterus, so that the minor fluctuations in the blood estrogen level will cause intermittent bleeding or spotting. Raising the blood estrogen level above the threshold with relatively small dosages prevents bleeding.

The earliest work on estrogen therapy indicated that patients with involutional melancholia would respond to estrogen therapy. The work of several psychiatrists seems to indicate that only occasionally does this condition respond to estrogen therapy.[51,71] Apparently the disparity in results depends to a certain extent on the diagnosis of this condition. It is possible that severe menopausal symptoms including depression may be interpreted as melancholia. On the other hand, some investigators considered that true melancholia is an irreversible condition due to degenerative changes in the brain, and that estrogen therapy does not affect the mental status although it may clear up subjective symptoms in these patients.

Reynolds and others[55] have shown that there may be certain psychogenic factors in the menopause apart from the vascular instability. Such patients do not respond well to estrogens.

Another psychic disorder which has been treated by estrogens is hypersexuality in males. Dunn[18] has demonstrated that 5 mg. daily of diethylstilbestrol decreased the libido in a hypersexual male but that the condition returned 9 to 16 weeks following therapy. This work might indicate that hypersexuality is actually due to an overproduction of androgen.

Considerable work has been done on the metabolic effects of estrogens. This involves especially changes in electrolyte balance, including calcium. It has been demonstrated that estrogens will induce retention of sodium and water in the body and that this retention follows usually the estrogen level of the blood. It was postulated by Greenhill and Freed[34] that premenstrual tension resulted from such a retention of fluids in the various organs giving rise to symptoms depending upon which organ was involved. They have administered ammonium chloride to combat the retention of fluid and have shown that the symptoms were dramatically relieved. Albright and associates[2] have studied the relationship of calcium metab-

olism to ovarian function. They have shown that there is a loss of calcium from the bone after ovarian failure and that many of the fractures of elderly women were due to the resulting porosity of the bone. They demonstrated that estrogen administration produces a more rapid healing of such fractures, due to the increased deposition of calcium in the bone.

Albright and workers[4] have demonstrated an interesting syndrome characterized by sexual infantilism together with dwarfism. This syndrome has also been described by Varney, Kenyon and Koch.[67] Treatment of this condition may be satisfactorily performed by estrogen.

Salmon and coworkers[58] have described a syndrome characterized by dysuria and incontinence in postmenopausal women due to atrophy of the urethral mucosa and impairment of sphincter function. Estrogen therapy brought relief to most of these patients, which was paralleled by growth changes in the vaginal mucosa.

Considerable interest has been aroused in the possibility of treating cancer of the prostate by endocrine preparations. Associated with this particular kind of malignant neoplasm there is often an increase in the acid phosphatase of the blood, especially if metastases have occurred. The administration of estrogens is followed by a reduction of this acid phosphatase and by an improvement in the clinical condition of the patient in the majority of cases. Huggins and associates,[40] who demonstrated that estrogens ("chemical castration") were of value in relieving the pain and bladder discomfort, also demonstrated the beneficial effects of castration in this condition. In a symposium at the 1942 A. M. A. Session, Alyea and Henderson[4a] claimed that castration caused marked improvement in many of these patients, as well as relief of pain from metastases, urinary obstruction and infection. Diethylstilbestrol was of value but not as effective. Creevy,[15a] however, was not as enthusiastic over these forms of therapy, but recognized them as palliatives in the late cases. Thompson[65a] considered orchidectomy and diethylstilbestrol as valuable adjuncts to prostatectomy. Nesbit and Cummings[48a] believed castration a worthwhile procedure in advanced cases when little aid was obtained from diethylstilbestrol therapy. Gutman[34a] regarded the data on diethylstilbestrol therapy as inconclusive. Apparently, dosage and appraisal of results are variables which must be controlled rigidly for better evaluation of the therapeutic response. The common factor in castration and estrogen therapy is the cancellation of androgen secretion of the testes which may stimulate the growth of prostatic cancer tissue.

Standardization. Several investigators have recently expressed the opinion that the therapeutic efficiency of an estrogen can be judged only by testing its potency in the human. Most claims for the relative therapeutic effectiveness of estrogens have been made on the basis of their activity as determined in laboratory animals, principally the rat or the mouse. The assumption that data so obtained can be accepted for the human has resulted in considerable confusion in the standardization of estrogen therapy. In the first place, results obtained from assays differ widely, as indicated by the fact that the rat unit of estrone as determined in different laboratories varies as much as several thousand per cent when compared to a weighed amount of crystalline material; the same holds true for assays in the mouse. The discrepancy in the assay of estrogens in the rat or the mouse cannot be entirely accounted for by technical differences in the performance of the assays, and it appears quite certain that each strain of rat or mouse has a different degree of sensitivity to any one estrogen. Similarly, comparisons of the potencies of different estrogens

such as estrone and estradiol in the same laboratory cannot be judged as the true reflection of the relative therapeutic potencies of these substances inasmuch as the ratios of activity as determined by different laboratories are far from constant. A recent article, a compilation of data on this subject reported by a number of investigators, illustrates the inconsistencies in animal assays and lead to the conclusion that any statement regarding the relative therapeutic activity of estrogens on the basis of animal assays is subject to considerable error, and assays in the human is at the present time the only hope for satisfactory therapeutic standards of estrogens.[21]

Several attempts have been made to assay the activity of estrogens in humans. Some investigators have utilized changes in the vaginal mucosa of menopausal patients following estrogen administration as an index of estrogen activity, much the same way as the castrate rodent is used. When it is recognized, however, that untreated menopausal patients have varying degrees of proliferation of the vaginal mucosa, it does not appear that this would be a satisfactory means of assay. There is a lack of evidence that the vaginal epithelium of a group of menopausal women will respond to a definite amount of estrogen with a sufficient degree of uniformity. Furthermore, the reading of vaginal smears in the human for assay purposes is liable to considerable experimental error. Several authors have expressed their dissatisfaction with the use of vaginal smears for assay purposes.[7,23] An attempt has been made to utilize the changes in the menopausal endometrium following estrogen administration as a means of assay.[69] Such a technique is not only cumbersome but is also open to more criticism than that mentioned above for the use of vaginal smears, inasmuch as untreated menopausal patients may possess sufficient degrees of endometrial proliferation and, in fact, hyperplasia.[49] This factor would interfere greatly with assays based on endometrial changes.

Bennett[7] has failed to find reliable data in human assays of estrogens based on four objective tests: 1, vaginal smears; 2, depression of gonadotropin excretion; 3, estrogen excretion; 4, changes in the cervical glands. He believes the subjective relief of menopausal patients the most reliable criteria. Mack and Ale[47] used the glycogen content of vaginal smears for assaying estrogens.

The author has selected the subjective response of menopausal patients as an end-point in the human assay of estrogens. It was acknowledged that the evaluation of such a response may be obscured by numerous uncontrolled factors. Nevertheless, this method has been selected for the assay for a number of reasons, not the least of which is the fact that the chief purpose in administering estrogens is to relieve the menopausal patient of her subjective symptoms. Such an assay requires no special technique and a large number of patients may be included in a study with little difficulty. In order to eliminate as many distracting factors from this study as possible, certain rules were established. Patients who complained of symptoms which were due to psychic changes due to environmental or social complications were not included in the groups tested. The patients treated, complained of at least two to four hot flashes daily together with other symptoms commonly found in the menopause such as nervousness, irritability and emotional instability. The psychic factors associated with any form of therapy involving subjective sensations were reduced to a minimum by eliminating any therapeutic suggestion such as a promise of beneficial results or leading questions concerning the therapeutic responses. In addition the subjective changes

of all the patients were evaluated in as constant a manner as possible. Furthermore, the estrogens were administered in several dose levels in the manner which is used for assaying estrogens in laboratory animals. Three synthetic estrogens, hexestrol, diethylstilbestrol and octofollin, were thus assayed. A satisfactory therapeutic dose of diethylstilbestrol is 0.5 to 1 mg. daily, hexestrol 2.5 to 5 mg. daily and octofollin 2 to 5 mg.[23,26]

Freed and associates[27] have also tested the therapeutic effectiveness of a natural estrogen which is administered by mouth. This preparation, called Premarin, is an extract containing the sulfate conjugated estrogens found in pregnant mare's urine which probably has the same proportion of estrogens as the non-crystalline estrogenic preparation in common use, but whose chief ingredient is estrone sulfate. Using the multiple dosage method with precautions mentioned, they have found that this substance is effective in the daily dosage of 1.25 mg. when administered in 3 doses. A somewhat different method is reported by the same group of workers for parenteral estrogen therapy, using the relief of subjective symptoms of menopausal women as a criterion of effectiveness. The estrogens were administered in substantial dosages at weekly intervals for 3 weeks. Therapy was then stopped and the period of relief from symptoms, taken to indicate the efficiency of the product. Non-specific factors were reduced by having the patients return at regular intervals and placebo injections administered in order to cancel out the psychic factor involved in performing injections. In this manner the authors have tested the potency of a number of estrogens, namely, estrone in aqueous suspension, estrone in oil suspension, diethylstilbestrol dipropionate and diethylstilbestrol dipalmitate.[24,25,26] By this method they showed that estrone in aqueous suspension was more effective than estrone in oil suspension and on the basis of laboratory investigation have concluded that the aqueous suspension was therefore more effective than estrone in oil solution. The data obtained by the same group of workers with diethylstilbestrol and the esters of this compound likewise demonstrate the greater effectiveness of the dipropionate and dipalmitate over the uncombined estrogen. It was conclusively demonstrated that the dipalmitate is considerably superior to the dipropionate when administered in quantities containing equal amounts of the free compounds. The authors concluded that this again demonstrates the inadequacy of applying laboratory data to human standardization of estrogens, inasmuch as, on the basis of laboratory experiments, the dipropionate should have been superior to the dipalmitate, the minimal effective dose of the former being about one-tenth that of the latter. Furthermore diethylstilbestrol dibenzoate which has a similar action to the dipalmitate in rats is considerably less effective in the human.

Androgens. The most efficient available androgen still remains testosterone propionate. This substance can be administered both hypodermically and in ointments. The compound methyl testosterone has been developed for oral use. Its potency by mouth is about one-third to one-sixth as great as a similar weight of testosterone propionate by injection. In choosing therefore the most desired androgen, the economic factors of each type of therapy must be evaluated, the relative low potency of the oral compound being weighed against the convenience of administration without the need of a visit to the physician. The use of pellets of testosterone or its compounds is the most efficient way of administering androgens. Such preparations, however, are not on the market as yet. Pellet implants produce an effect which acts over long periods of time without

the need of additional therapy. As a rule, 500 to 1000 mg. of testosterone divided into 4 to 5 pellets and implanted appears to be a satisfactory dose. Biskind and his coworkers[10] prefer methyl testosterone pellets because of economy and easier handling in sterilizing the material. For percutaneous administration an effective dosage of testosterone is approximately 15 to 25 mg. daily in an ointment with a lanolin base.

Androgens have been recommended for a number of conditions. There seems to be little doubt that they are satisfactory in replacing the endocrine activity of the testis. Castrate or eunuchoid males may be restored completely to masculinity except for spermatogenic activity. The response of such patients to androgens is well known and need not be described except briefly. The following reactions occur from the administration of androgens to hypogonadal males: increase in blood volume, flushing of the skin and deepening of color, increase in melanin of the skin, growth of the penis associated with sexual activity, stiffening of the beard and an increase in hair growth on the trunk and limbs, genital enlargement, including the skin of the scrotum, a deepening of the voice, and the development of other masculine characteristics. There is also an increase in body weight associated with water retention as well as nitrogen, a slight increase in basal activity, closure of the epiphyseal lines in adolescents, increase in cardiac output, and development of acne. An overdose of androgens may result in the following complications: edema of the lower extremities, bilateral enlargement of the breasts, priapism, precocious maturity in adolescents, and excessive acne. Most of these reactions are reversible and there is a return to the original condition within a few weeks following cessation of therapy. The average dose of testosterone propionate in replacement therapy is about 75 to 150 mg. weekly. Methyl testosterone is usually administered in dosages of 30 to 90 mg. daily. It is claimed that the administration of bile acids enhance the oral effectiveness of the androgens. In addition to treating outspoken cases of testicular failures, androgens have been used in the therapy of functional cryptorchidism. Moderately satisfactory results have been obtained with such therapy, but it appears that the use of chorionic gonadotropin is more effective than androgens.[30]

Considerable publicity has been given to the use of androgens in the male climacteric.[17] This condition is rather vague because of the lack of criteria for determining the symptoms of this condition and because of the extreme variability in the age at which there is a decline of sexual powers in males.[36] It is generally thought that hot flashes, nervousness, irritability and other symptoms characteristic of female menopause are also seen in the male climacteric. It is acknowledged that such a set of symptoms are found only rarely in men. However, a few cases have been reported in which such symptoms are found and these have responded to androgen therapy. There is still inadequate evidence that androgens are of any value in senile impotence or in premature impotence without organic cause. There may be temporary benefits which are probably on the basis of suggestion. In regard to psychic impotence, Carmichael and Noonan[14] find that this substance is of limited value and that beneficial responses are of non-specific nature Involution melancholia in males and androgen therapy have the same status as estrogen therapy in women with this condition. Pardoll and Belinson[51] showed that androgens improved the bladder function and increased the skin temperature but have little effect on the mentality of such patients. It is of significance that Kenyon and others[43] have shown that testosterone propionate has a metabolic

effect on senile males much the same as it does on younger men who are not castrated. In the treatment of male homosexuality, it has been shown through the use of androgens that little reversal of the sexual tendency is encountered.

The action of testosterone therapy on somatic growth has been shown to be of considerable importance. This work has been developed from the experiments of Dorf, and others, who showed that chorionic gonadotropin therapy in young boys resulted in an increase in skeletal development. This effect is believed to result from androgen liberation of the testes. Androgen therapy has an effect on epiphyseal closure but nevertheless it has a powerful effect on causing bone growth under certain conditions.[53,73] Finkler and others[20] have shown that androgen therapy in hypogonadal boys produces a significant growth increment. Kenyon[42] and associates have suggested that this growth may be related to the retention of protein generally throughout the body.

Walker[68] and others[35,45] have demonstrated that androgen therapy may be of value in the treatment of angina pectoris. It has been claimed that such therapy induces a drop in blood pressure where there is hypertension. The ability to perform more work without chest pain and a greater sense of well-being results. Many of these patients who were benefited showed definite changes in the electrocardiogram. Nevertheless, although Goldman and Markham[31] have obtained beneficial results in treating climacteric males with angina, they concluded that their cases could be considered to have the effort syndrome and that there were no actual cardiac lesions. The effect of the androgens in causing an increase in hemoglobin, stability of the peripheral vascular system as well as the psychogenic control of the cardiovascular apparatus may well play rôles in the relief from anginal pain. Testosterone may be of some benefit in renal disease since it has been demonstrated that testosterone neutralizes the action of certain kidney poisons, and increases the survival of animals whose ureters have been ligated.[63]

Albright, Parson and Bloomberg[2] have obtained dramatic results in the androgen therapy of Cushing's disease or adrenocortical hyperactivity. There was in such patients a return of muscular strength, increase in weight, decrease in redness and bruisability of the skin, and a feeling of well-being. These changes were associated with a retention of nitrogen, phosphorus and calcium. Estrogens were ineffectual while progesterone was only of slight value in these cases.

Androgen therapy in hypertrophy of the prostate was received with enthusiasm at first with claims of subjective improvement and relief from bladder discomfort. More recent investigations have discounted the value of this therapy and others have questioned the wisdom of delaying surgery by such a procedure. Even though there may be an apparent improvement, the prostatic hypertrophy is actually not reduced. Where bladder discomfort is due to an atrophic prostate, androgen therapy may afford temporary relief.

The androgens have been used widely in the treatment of gynecologic conditions. This has been reported by a number of workers.[28,59] The chief danger in such therapy is the induction of virilism in women who have received excessive amounts. The androgens have been reported of value in treating functional bleeding as well as bleeding associated with fibroids. Testosterone proprionate, 250 to 400 mg., is capable of completely suppressing a menstrual period. Lesser amounts delay the onset of menses. The exact mechanism of this response has not been established. It has been

postulated that the androgens may either neutralize the estrogen output of the ovaries or inhibit the anterior lobe gonadotropin secretion which controls ovarian activity. Similarly, patients with dysmenorrhea have derived some benefits from androgen therapy. Injections of 150 to 400 mg. of testosterone throughout the month are necessary to relieve this condition. Greenblatt[32] has reported that androgens are able to stimulate the libido in women who are frigid as well as to increase the libido in normal women. Greenblatt recommends the implantation of pellets for gynecologic conditions. He has also reported that certain conditions of bladder dysfunction with frequency and incontinence may be dramatically relieved with androgens. These women usually had fibroid tumors of the uterus but apparently the effect of the steroid could not be attributed to decrease in size of the tumor. He believes that the genito-urinary tract is under the influence of hormones which may also account for the changes in these tissues found in pregnancy. Androgens have also been recommended for the treatment of menopausal symptoms where estrogens are contraindicated as in cases in which there is a personal or familial history of mammary cancer. Other gynecologic conditions which have responded to androgen therapy include painful breasts due to chronic cystic mastitis, premenstrual tension, afterpains and suppression of lactation. Attempts to reduce the size of fibroids have been partially successful but of doubtful practicability.

As a rule androgen therapy for gynecologic conditions is most efficient in the hands of specialists.

Hamilton[37] discussed in detail the rôle of androgens in acne. The therapy of this condition from the standpoint of endocrines is not yet established.

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RADIOLOGY

UNDER THE CHARGE OF

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SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

ANGIOCARDIOGRAPHY

By Harry M. Weber, M.D.

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That Roentgen rays would one day prove to be of immense value in the study of the heart and of the circulation seems to have been appreciated since the very beginning of the Roentgen era. Holzknecht was able to bring out a report concerning his observations on the heart in health and disease as early as 1901, 6 years after Roentgen announced the discovery of the type of radiation now bearing his name. A considerable

body of knowledge and experience has been accumulated down the intervening years, and for many years the roentgenologic method has been regarded as an important, even an indispensable, part of the routine clinical study of the heart and great vessels of the thorax. Even among clinical cardiologists it ranks in value immediately after the history and the physical and electrocardiographic examinations. While it is true that certain normal and abnormal conditions of the heart and great thoracic vessels can be determined with accuracy and precision during life only with the use of roentgenologic methods, and that certain others are determined more accurately and with greater facility with these methods than with others, it must be accepted that, as with electrocardiography, there are important cardiovascular abnormalities which exhibit no roentgenologic evidence of their existence at all. Some of these are too small or too new to produce demonstrable changes in the general configuration of the cardiovascular silhouette; and changes in the muscular activity, if present at all, are so minor as to escape even the most refined methods of roentgenologic detection. For the most part, too, the roentgenologic diagnostic elements of cardiovascular disease are not direct, but indirect and inferential in character. Roentgenologic cardiovascular diagnosis is largely a deductive process, the observer using such anatomic changes as enlargement or deformity of the whole or some portion of the cardiac and vascular shadows, abnormality of cardiovascular pulsation, and displacement or distortion of neighboring or contiguous anatomic structures as the premises for his diagnostic deductions. This is because the image of the heart obtained by conventional roentgenoscopic and roentgenographic technique is a composite one and not always analyzable with certainty; and, although the aorta can usually be visualized fairly well, the other large vessels of the thorax are seen but indistinctly when seen at all. The roentgenologic method applied to the diagnosis of other tubular and saccular viscera has been rewarded with greater diagnostic success. This appears to be chiefly because it has been possible to enhance their roentgenologic contrast with the use of radiopaque substances to opacify* them, on the one hand, or with the use of innocuous gases to make them more radiolucent than the surrounding tissues, on the other. The diagnostic yield of the roentgenologic method applied to the alimentary and urinary tracts, and to the respiratory and central nervous systems may truthfully be said to be the greater the easier it is to apply contrast roentgenography and roentgenoscopy to them. Until relatively recent times, no practical way of visualizing the heart and great thoracic vessels had been evolved.

In 1938, Robb and Steinberg[5] first described a new and practical method of rendering opaque the chambers of the heart and the large intrathoracic blood-vessels sufficiently to be studied on roentgenograms and on the roentgenoscopic screen. The method they described consisted of two essential procedures: 1, a rapid intravenous injection of a large enough volume of highly concentrated but relatively innocuous radiopaque solution to make the chambers of the heart and the larger intrathoracic blood-vessels opaque to the Roentgen rays during the first circulation; and, 2, roentgenography or roentgenoscopy at the very moment these structures are so rendered opaque. Obviously, the interval between the injection of the solution and its arrival in the thoracic blood-vessels and in the various

* We are glad to accept this neologism as filling a gap for which there will be increasing need in radiology, to be used in the same way as such words as "liquefy" and "solidify," of ancient and honorable standing. We are curious to see, however, whether "lucify" and others yet unborn will also be found to be needed and therefore desirable.—EDITOR.

parts of the heart would be very short, especially for its arrival in the superior vena cava, the right cardiac chambers and the pulmonary vessels, but the interval, in most instances, would also be quite constant. It could be shown, too, that a longer and more variable period of time would be required for the injected contrast solution to reach the left cardiac chambers and the thoracic aorta. Accurate estimation of these intervals had to be made, and for this purpose Robb and Steinberg[5] made practical use of the methods of Hitzig[3] and of Robb and Weiss[9] of determining the circulation times between the arm and pulmonary capillaries and between the arm and the carotid sinus respectively. They found that the superior vena cava, its larger tributaries, and the right atrium were radiopaque in $1\frac{1}{2}$ seconds after the beginning of the injection, the right ventricle and the pulmonary arteries in about 3 seconds, the pulmonary veins and the left atrium in from 6 to 8 seconds, while it took from 8 to 10 seconds for the contrast solution to reach the left ventricle and the aorta. The position of the patient in relation to the Roentgen ray tube and film also had to be determined before injection was begun, and it would vary, of course, with the structures the observers wished to visualize. This posing was done under roentgenoscopic control. In their original work, Robb and Steinberg used an ordinary stereoscopic cassette changer to obtain 2 roentgenograms in rapid succession. They were able to make visible the right side of the heart and the pulmonary arteries practically every time they tried to do so, but they were not quite so consistently successful in obtaining a satisfactory visualization of the left chambers of the heart and the aorta.

They used the contrast substance diodrast (3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine), which contains 49.8% of iodine. It was prepared in 70% solution. It was found to be the most satisfactory of all available similar drugs, because it mixes freely with the blood, is eliminated quickly, is inert, is relatively non-toxic, and is non-irritating except rarely at the site of injection in a few cases. Other radiopaque substances like skiodan (an iodomethane sulfonate of sodium) and hippuran (a sodium salt of ortho-iodo-hippuric acid) also were given consideration, but they were found to cause unfavorable reactions when administered in sufficient quantity and concentration. The dose of the radiopaque drug had to be varied to some extent with the size and weight of the patient and also with the part that the observer wished to visualize. As the observations were extended, it was found that while a 70% concentration was the most satisfactory for all purposes, concentrations as low as 40% could be used for opacifying the superior vena cava, the right side of the heart, and the pulmonary vessels. The injection was made into an antecubital vein, and had to be made rapidly. Robb and Steinberg procured a special transfusion needle with an exceptionally large bore to increase the speed of injection. They found that in the average case 35 cc. of the 70% solution (24.5 gm. of diodrast) was needed to opacify the left chambers of the heart and the thoracic aorta, and 25 to 30 cc., to visualize the pulmonary blood-vessels. For subjects with a large thick thorax, or with cardiac enlargement, or with pulmonary congestion, larger quantities were found to be necessary. The dose was found to vary between 25 and 45 cc. of the 70% solution. The solution must be injected in 2 seconds or less, and this rate of injection seemed to cause little difficulty in the average case. In general, the immediate reaction of patients to the injection was mild and transient even in cases in which the patients were quite ill, and there were no serious delayed effects. No fatality or other serious consequence was experienced.

These are the fundamental aspects of angiocardiography. Robb and Steinberg,[6,7] the originators of the method, described in two articles the technique of injection and of roentgenography in minute detail, outlined precautions to be observed, and indicated the contraindications to the use of the method. These papers are required reading for anyone who wishes to make practical use of the method.

Apparently, the outstanding technical difficulty attending practical application of angiocardiography is that of establishing the precise interval when roentgenographic exposures are to be made after injection of the contrast solution has been begun. Sussman, Steinberg and Grishman[15] have called particular attention to this point. They suggested the use of the conventional radiographic polygraph with which multiple exposures can be made on a single film as rapidly as the polygraph tray can be shifted. They also suggested that theoretically, at least, the best angiocardiographic method would be a motion picture of the roentgenoscopic screen made continuously while the opaque blood was passing through the cardiovascular and pulmonary circuits. They tried this with success, as Stewart and his associates[14] also had done. This procedure, however, had the practically insuperable disadvantage of demanding a special and very expensive high-speed photographic lens, not generally available. Another objectionable feature lay in the circumstance that a very rapid and sensitive, therefore, coarsely grained photographic emulsion was required, and this brought with it too much loss of photographic detail. As a compromise, Sussman and his associates[15] tried and recommended the use of a "still" camera equipped to make multiple exposures of the roentgenoscopic screen in rapid succession. Using a commercially available roentgenoscopic screen and photographic film, *f*1.5 or *f*2 camera lenses, and a rotating target Roentgen ray tube, these observers found that a minimum of 10 exposures could be made during a period of observation extending over 8 seconds. In this way it became possible to get as many as 16 exposures in the 8 or 10 second interval during which the contrast solution was passing through the cardiovascular and pulmonary circuits, instead of 2 or at the most 4 when cassettes were used. No longer was it necessary to calculate the circulation time except when there was reason to suspect considerable prolongation. The roentgenoscopic screen could be observed during the actual time of photography so that exposures could be continued until part or all of the circuit was completed, and the patient could be posed under direct vision. The cost of the apparatus was relatively small, that of the photographic film negligible.

A disadvantage arose, however, in connection with this approach also. This time it had to do with the coarse grain of the roentgenoscopic screen recorded on the photographic film—especially disturbing when the 35 mm. film was projected or magnified. Direct roentgenography with the same rapidity of exposure would be advantageous in many ways, the investigators thought, particularly to visualize small structures of slight density. Sussman, Steinberg and Grishman[16] soon were instrumental in having an ingenious apparatus designed and constructed with which 8 direct roentgenograms of excellent quality could be produced in the short interval of time required for angiocardiography. It was a wooden wheel 62 inches (127 cm.) in diameter, mounted on an axle, and carrying eight 10 by 12 inch (25.4 by 30.4 cm.) cassettes mounted on its periphery. The wheel is rotated manually behind a screen of lead provided with an opening 10 by 12 inches (25.4 by 30.4 cm.) in size, behind which each cassette passes. A door stop halts the wheel as each cassette arrives in position

behind the aperture in the screen of lead. The patient is posed beforehand by roentgenoscopy, one cassette being removed and replaced by a fluorescent screen. The inventors of this device visualized mechanical improvements which would make automatic rotation and automatic exposure possible. In this way, errors inevitably attending hand operation could be eliminated, and the 8 exposures could be obtained in a shorter and still more advantageous period of time. Schwarzschild[10] regarded the apparatus just described as large and unwieldy, so he set about devising another which he claimed had the advantage of greater ease of operation, diminished requirements of space, and a mounting which made it possible to adjust the apparatus for height, a convenience which the apparatus of Sussman and his associates did not seem to possess. Essentially it is a rectangular box divided into 3 compartments in line. One of the compartments receives the unexposed cassettes, in the second the cassettes are exposed, and the third receives them after exposure. A fluorescent screen is mounted in the second compartment so that the patient can be posed under roentgenoscopic control. The cassettes are shifted from one compartment to the others by means of a thrust bar, connected electrically with the Roentgen ray timer, and the arrangement is such that when the thrust bar is withdrawn the timer circuit is closed and the exposure is made. A device is also incorporated in the apparatus by means of which the time of exposure is recorded on each film. According to the designer, 7 exposures in 6 seconds can be made with this machine without difficulty, and it is anticipated that a greater number will be possible with more finished construction. Thus it is apparent that as time goes on the technical handicaps of angiocardiography are being overcome one by one, and the result is sure to be a more general use of the method and a more profound appreciation of its diagnostic potentialities.

What has been the diagnostic yield of angiocardiography so far? The originators could foresee that an important practical application would be found in the study of congenital disease of the heart, and they were the first to make observations on this cardiovascular anomaly. Early in their experience with this new method of investigation, they reported that while they had not yet been able to get direct visualization of the abnormal communication in cases of interatrial and interventricular septal defects, or in cases of patent ductus arteriosus, they[8] did obtain satisfactory indirect evidence of the defect in the first-named disorder and the last, by observing recirculation of the opacified blood, and in the cases of interventricular septal defect by noting selective enlargement of the ventricles and of the pulmonary artery. They also were able to demonstrate, in cases of coarctation of the aorta, the constricting deformity of the aorta and the collateral circulation developed as a result of it.

Grishman, Steinberg and Sussman[1] also published observations on 2 cases of coarctation. In the first case the narrowing in the proximal descending aorta was demonstrable, the aorta immediately above and below the constriction was normal, the left ventricle was dilated and hypertrophied, and the right internal mammary artery was dilated. The clinical findings in this case were typical, but corroborative roentgenologic evidence was lacking without contrast visualization. In the second case, a complicated one, the patient had extreme hypertension, cardiac murmurs, lowered blood pressure in the legs, differences in blood flow in the upper and lower extremities, no evidence of renal disease, and roentgenographically demonstrable notching of the ribs which suggested coarctation. There also were signs of exophthalmic goiter. Angiocardiographic

examination revealed a constriction of the descending aorta below the exit of the left subclavian artery, marked hypertrophy of the left ventricle, and a dilated supracardiac aorta.

These investigators[2] also studied a case of the tetralogy of Fallot, and were able to get visual evidence of each one of the classic anatomic features of the syndrome: stenosis of the pulmonary artery, dextroposition of the aorta, interventricular septal defect with right-to-left shunt, and hypertrophy of the left ventricle. Pursuing the study of congenital heart disease, the same observers[12] have published observations on 3 cases of dextrocardia showing how contrast visualization can be made to prove the actual anatomic relationships both in true dextrocardia with *situs inversus* and in the several anatomic varieties of dextroposition of the heart.

Robb and Steinberg[8] also reported observations made on patients with acquired heart disease. In cases of rheumatic mitral stenosis and insufficiency, they found, among other things, that the prominence of the pulmonary arc in the frontal view was caused not by the enlarged pulmonary conus or the left atrium, but solely by the dilated pulmonary artery, that the exaggerated hilar and pulmonary roentgenographic markings were the shadows of engorged blood-vessels, and that the left auricle formed the convexity immediately below the pulmonary arch. In syphilitic aortitis it was possible to make visible the infracardiac portion of the aorta, an observation heretofore impossible to make, but important because this portion is the site most frequently involved with syphilitic changes. It was also possible to determine the exact site, size and shape of aortic aneurysms. In hypertensive heart disease it was possible to demonstrate the degree of hypertrophy and dilatation of the left ventricle, the torsion and unfolding of the aorta, "buckling" of the innominate artery, and the left subclavian artery forming the anterior boundary of the "aortic triangle." In arteriosclerotic cardiovascular disease little in the way of cardiac change was demonstrable, but it was possible to show several kinds of pathologic change in the aorta, even when there had been no hypertension, circulatory failure or coronary thrombosis. In one case, the presence of a pericardial effusion was proved beyond reasonable doubt by showing that the cardiac chambers were within normal limits of size in a cardiac silhouette markedly increased in size.

In cardiovascular changes existing in various chronic pulmonary diseases, such as pulmonary tuberculosis, bronchiectasis, bullous and generalized emphysema, and primary carcinoma of the bronchus, Robb and Steinberg[8] elicited evidences of pathologic change that were both interesting and important. They concluded that the greatest value of angiocardiography in this field was in disorders near the hilum, which often cause great diagnostic difficulties. Hilar masses, they said, can be distinguished from the neighboring blood-vessels, and their site and configuration determined from the vascular compression and displacement they produce. Steinberg, Robb and Roche[13] were able to demonstrate the value of the method for this purpose very vividly.

Sussman, Steinberg and Grishman,[17] in a study of the heart and great vessels in emphysema, noted evidence of right ventricular strain in 24 of 28 unselected cases of pulmonary emphysema of various etiologic types. The principal criteria for right ventricular strain were enlargement of the cavity of the ventricle, dilatation of the pulmonary artery, and convexity of the interventricular septum to the left. In 12 of the 28 cases, there was definite dilatation of the right ventricle, and in 12 others, dilatation of this chamber was called probable. In only a few of the 24 cases did the stand-

ard roentgenologic examination of the thorax or the electrocardiographic examination give evidence of enlargement of the right side of the heart, although it should be noted that it is notoriously difficult to detect minor degrees of enlargement of the right side of the heart in the teleoroentgenogram. In 2 of the cases, both with marked emphysema of long duration, there was no right ventricular dilatation, and Sussman and his associates offered no explanation of this finding. The angiocardiographic findings were also correlated with the electrocardiographic findings, and in 13 of the 24 cases of definite or probable enlargement of the right ventricle the electrocardiogram was normal. The lack of right axis deviation in some of the cases was assumed to be due to the coincidental presence of left ventricular enlargement resulting from some other type of heart disease. Finally, Steinberg and his associates[11] applied the angiocardiographic technique to the study of a case of arteriovenous fistula involving the third portion of the left subclavian artery, and they said that the procedure is especially well suited for localizing arteriovenous fistulas involving the large vessels near the heart.

Contrast visualization of the heart is undoubtedly here to stay. It has already made important contributions to medical knowledge and there is promise of even more in the future. Although the method is safe and practical, it is one that demands a high degree of teamwork and a great precision in technique. It will be most productive of good diagnostic results in the hands of those already well grounded in other methods of cardiovascular diagnosis. Not all patients with cardiovascular disease should be subjected to it, rather let it be reserved for those who present unusually difficult diagnostic problems not readily solved by the older and more familiar methods of cardiovascular diagnosis.

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PHYSIOLOGY

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Capillary Permeability to Horse Protein in Burn-shock. MARTIN NETSKY and SAMUEL LEITER (Harrison Department of Surgical Research Schools of Medicine, University of Pennsylvania). The time and rate of

appearance in lymph of intravenously injected horse serum was used as a measure of capillary permeability in dogs. Since the horse serum was injected intravenously, its appearance in lymph represented direct passage across the capillary endothelium. Data obtained on 3 normal and 3 burn-shocked dogs form the basis of this report. Dogs under morphine-barbital anesthesia were closely clipped from feet to axillæ. The cervical lymph ducts and the left thoracic duct were cannulated. Two cc. of horse serum per kilogram of body weight were injected intravenously. The body was then immersed up to the axillæ in water at 72° C. for 60 seconds. The time of appearance and the concentration of horse serum in lymph was determined by precipitin reaction with rabbit anti-horse serum, and the washed precipitate was read turbidimetrically with the Klett-Summerson colorimeter. Protein levels in blood and lymph were determined by the biuret method of Kingsley. In normal animals, it was found that horse serum appeared sooner, at a greater rate, and reached higher levels in thoracic duct than in cervical lymph, thus giving evidence that the thoracic drainage area is more permeable than the cervical drainage area. Following the burn, changes in capillary permeability were noted promptly in both the burned (lower body) as well as the non-burned (head and neck) area. In the normal dog, horse serum appeared in cervical lymph in 50 to 100 minutes. Following the burn, it appeared in 10 to 20 minutes. Similarly, horse serum was detected in thoracic lymph of the normal dog in 20 minutes, whereas it appeared in the burned dog almost immediately following the burn. The shape of the time-concentration curve for horse serum was altered in both areas by the burn. Total lymph protein concentration was not increased during the 3-hour observation period.

An Investigation on the Origin of Glycoside Emesis. MELVIN DRESBACH (Department of Physiology and Harrison Department of Surgical Research, University of Pennsylvania). As reported in previous preliminary communications (*Am. J. Physiol.*, **126**, 480, 1939; **133**, 264, 1941; *Fed. Am. Soc. Exp. Biol.*, **1**, 22, 1942), chemically pure cardiac-active glycosides produce nausea and vomiting in cats and dogs after extensive interference with the afferent innervation of one or more of the viscera. It has also been found that such reactions can be elicited in the animals after surgical interruption of all known visceral afferent fibers collectively (technic described briefly in the above publications). In a group of 4 dogs and 1 cat thus prepared, ouabain, lanatosides A, B and C, k-strophanthoside, thevetin, an aglycone (strophanthidin) and apomorphine HCl induced emetic responses which were definite, though necessarily incomplete, vomiting acts. The doses required were sometimes not significantly larger than the preoperative amounts and the latencies of the responses were, for the most part, of the same order as those in the unoperated animals. When a single dose of any glycoside was given by a parenteral route insuring rapid entrance into the blood stream the supplemental amount of strophanthidin necessary to evoke emesis had to be increased in the succeeding hours or days in order to obtain the reaction. This result was interpreted to mean that the subemetic action of the glycosides continued for a period, the length of which depended, in part, upon the individual one and the amount of it administered. Inasmuch as definite evidence, according to the author's knowledge, is lacking that these substances ever excite vomiting by their action on any peripheral neural

structure in the head or neck, it would seem that in the animals described, the seat of the emetic stimulation and the persistence of the action was a central one; but other interpretations are conceivable (the paper was illustrated by lantern slides and a motion picture of the vomiting in the cat after visceral deafferentation).

The Effect of Replacement of Normal Blood by Erythrocytes Saturated With Carbon Monoxide. DAVID L. DRABKIN, FREDERIC H. LEWEY, SAMUEL BELLET and WILLIAM H. EHRICH (Departments of Physiological Chemistry, Neurosurgery, Cardiology, and Pathology, University of Pennsylvania). In one group of dogs severe carbon monoxide poisoning was produced by inhalation of sufficient carbon monoxide to reach "critical" levels of 75% HbCO. After a certain length of exposure under these conditions the animals collapsed with evidence of cardiac and respiratory failure. In those animals which survived extensive necrotic changes were found in the brain (cortex) and heart.

In another group of dogs, levels of 75% HbCO were obtained by replacement of the blood with washed erythrocytes saturated with carbon monoxide (96% HbCO). In these animals no signs characteristic of anoxia (R–T elevation in the electrocardiogram, slowing of conduction, and heart-block) were observed. Necropsy revealed no evidence of myocardial or cerebral damage. Following termination of the transfusion of HbCO containing cells, the percentage of carbon monoxide in the blood decreased approximately 2 times more rapidly than in the dogs poisoned through the respiratory route.

Except for the similar percentage of HbCO in the blood, the two experimental states differ markedly. The partial pressure of carbon monoxide to which the tissues are exposed is very probably greater in the dogs which inhaled the gas. The undetermined factor of tissue poisoning may therefore be operative to a far greater extent in the animals severely poisoned through the respiration.

A more obvious explanation of the results may be the operation *in vivo* of the Haldane and Stadie and Martin effect, previously established *in vitro*. This effect may be described as follows: Partial poisoning of the four iron atom hemoglobin molecule with carbon monoxide results in molecular species which hold the remaining oxygen more tightly. This induced greater affinity, for oxygen decreases the "oxygen unloading capacity" at the tissues. From the dissociation curves of non-poisoned $Hb_4(O_2)_4$ and 75% poisoned $\begin{matrix} Hb{-}O_2 \\ | \\ Hb_3{-}(CO)_3 \end{matrix}$ at 10 mm. pO_2, it is calculated that the "functional" hemoglobin (upon the basis of normal unloading capacity) in the latter case is not 25% but only 11%. This presents a clearer view of the meaning of the "critical" level of 75% HbCO in the animals which inhaled the gas. On the other hand, in the transfused dogs a state approaching 75% of $Hb_4(CO_4)$ and 25% of "functional" $Hb_4(O_2)_4$ was attained. Opportunity for appreciable equilibration of the unpoisoned $Hb_4(O_2)_4$ as the carbon monoxide dissociated *in vivo* from the $Hb_4(CO)_4$ was not afforded due to opposing rates of rapid "blowing off" of CO in the lungs and relatively slow uptake of CO by the hemoglobin. The element of time here operates presumably in such a way that the pCO built up in the plasma is appreciably lower than in dogs poisoned through the respiratory route.

The much more rapid decrease of HbCO in the blood of the transfused animals is also explainable by the operation *in vivo* of the Haldane effect.

It may be added that the transfusion of the HbCO containing cells often prevented imminent circulatory failure attendant upon the severe bleeding procedure in the "replacement" experiments. These studies have suggested the probable value of prompt transfusion of normal blood in dogs severely poisoned through the inhalation of carbon monoxide. Transfusion of normal blood has been tested, and found effective under appropriate conditions.

Intravenous Ammonium Chloride for the Treatment of Alkalosis. H. A. ZINTEL, J. E. RHOADS, and I. S. RAVDIN (Harrison Department of Surgical Research, University of Pennsylvania). The need for a more effective parenteral method of correcting alkalosis has arisen with increasing frequency since the introduction of continuous suction drainage in the preoperative preparation of patients with pyloric obstruction. Sodium lactate has been administered intravenously for the correction of acidosis, but no preparation has been generally available for the parenteral treatment of alkalosis.

Although the kidneys will usually restore the electrolyte pattern of the plasma, if sufficient fluid and salt are provided, there remains an occasional patient who does not respond to this type of therapy. It has been demonstrated that postoperative patients and patients with pneumonia are often unable to excrete excess sodium.

Intravenous ammonium chloride was administered 12 times to patients with severe alkalosis. Although our experience has been too limited to establish firmly the safety of the method, its use is justified when the intravenous administration of sodium chloride and fluid has restored the serum chlorides and total serum base to normal, but has failed to overcome the alkalosis.

No serious reactions have occurred when a 2% ammonium chloride was administered in a 5% glucose solution intravenously. The response to this therapy is quite uniform. One gram of intravenous ammonium chloride reduces the serum CO_2 of an 150 pound adult approximately 1.1 vol. %.

BOOK REVIEWS AND NOTICES

First Aid and Bandaging. By Arthur D. Belilios, M.B., B.S. (Lond.), D.P.H. (Eng.), and others. Pp. 628; 239 figures. Baltimore: Williams & Wilkins Company, 1942. Fourth reprint. Price, $1.75.

Like Hammer's Advanced Handbook, this book is written by English authors who should have had much practical experience in the last few years. It begins with an excellent chapter on General Principles. Consideration of the general structure and functions of the body are condensed into 10 concise and pertinent pages. The 20 pages devoted to the skeleton follow later, just before fracture; and so on with the other body systems. One naturally finds minor differences in terms and procedures from those in use in this country (especially to be regretted is the omission of "the fireman's lift" from the methods of transport by the single helper); but on the whole the book should be warmly recommended. E. K.

Military Surgical Manuals. IV. Orthopedic Subjects. Prepared and Edited by the Subcommittee on Orthopedic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 306, 79 figures. Philadelphia and London: W. B. Saunders Company, 1942. Price, $3.00.

This volume is the fourth of a series designed to furnish the medical departments of the United States Army and Navy with concise presentations of necessary information in the field of military surgery. Its four sections cover ununited fractures, injuries of the spinal column, compound fractures, and osteomyelitis. In general, its subject material is limited to orthopedic surgery and its military application. No discussion of simple fractures, dislocations (except those of the vertebral column), and sprains is given, and the subject of amputations is only briefly treated. This volume will have only limited application for those not in the armed forces. M. T.

The Vertebrate Eye. By Gordon Lynn Walls, Research Associate in Ophthalmology, Wayne University College of Medicine. Pp. 785; 197 figures (3 in color), numerous plates and tables. Bloomfield Hills, Mich.: Cranbrook Institute of Science, 1942. Price, $6.50.

This is the most important book on the subject to appear in the last few years. Dr. Walls has indeed knowledge of the comparative morphology of the vertebrate eye and from this he has traced the evolutionary changes which have led to functional specialization throughout the vertebrate series. The book is logically organized into three sections. In the first part the human eye is dealt with and an excellent résumé is given of the physiology of the duplex retina. Most of the recent developments in this field are well recounted, perhaps only lacking in an adequate presentation of the electrical phenomena which accompanies retinal stimulation. The second and third part are comparative morphology and show how various structures in the eyes of the vertebrate series have been developed to meet the needs of the particular animal.

The style is exceedingly readable and the author manages to retain one's interest throughout. Considerable praise should also be given to the publishers for the excellent type and illustrations, the beauty and perfection of which add much to the book's enjoyment. The book cannot be too highly recommended and should be owned by everyone interested in the eye.

F. A.

NASAL MEDICATION—A PRACTICAL GUIDE. By NOAH D. FABRICANT, M.D. Pp. 113; 20 illustrations. Baltimore: The Williams & Wilkins Company, 1942. Price, $2.50.

THIS book in a condensed form presents the more important facts of nasal anatomy and physiology. Particular stress is placed upon nasal ciliary action and hydrogen ion concentration of nasal secretions. The best medicaments and methods of application for both acute and chronic disease are discussed. This work is of decided value to anyone interested in this type of therapy.

K. H.

DISEASES OF THE BREAST. By CHARLES F. GESCHICKTER, M.A., M.D., Lieut. Commander, Medical Corps, U. S. Naval Reserve, Director of The Francis P. Garvan Cancer Research Laboratory, Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in Collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School, Visiting Surgeon and Assistant Oncologist, University Hospital, University of Maryland Medical School, Visiting Oncologist, Baltimore City Hospitals. Pp. 829; 593 illustrations. Philadelphia: J. B. Lippincott Company, 1943. Price, $10.00.

THE greater part of this book deals with an analysis of clinical and pathologic data of some patients seen by the author and some from the surgical wards of Johns Hopkins Hospital, and of data collected by Drs. Bloodgood, Halsted and Welch, and others in the Surgical Pathological Laboratory of Johns Hopkins Hospital.

Over 2500 cases of breast cancers are analyzed, 1200 cases of mammary dysplasia, many benign tumors, and a variety of the rare conditions which affect the breast. There is detailed discussion of the clinical aspects, treatment, analysis of end-results, and of the gross and microscopic changes. There are many excellent illustrations, charts and tablets. Often photographs of the patient and the gross specimen and a photomicrograph are effectively used in correlating the pathologic changes with the clinical.

Considerable emphasis is placed on the endocrine factors involved in the etiology and treatment of breast diseases. In this connection are described experiments by the author on the production, by administration of estrogenic substances, of various pathologic changes in the mammary gland of rats, and comparisons are made of these changes with those found in patients. From this is elaborated a theory of how pathologic changes occur in the human breast.

The book is essentially a presentation of information derived from the author's personal experience and an expression of personal interpretation placed in relation to the views of others. The book contains a wealth of data, interesting and useful to both clinicians and pathologists.

I. Z.

LYMPH NODE METASTASES. By GRANTLEY WALDER TAYLOR, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Associate Visiting Surgeon, Massachusetts General Hospital; Surgeon, Collis P. Huntington Memorial Hospital and Pondville Hospital, Massachusetts Department of Public Health; and IRA THEODORE NATHANSON, M.S., M.D., Instructor in Surgery, Harvard Medical School; Assistant Surgeon, Collis P. Huntington Memorial Hospital, Beth Israel Hospital and Pondville Hospital, Massachusetts Department of Public Health; Assistant in Surgery, Massachusetts General Hospital. With a Foreword by SHIELDS WARREN, M.D., Assistant Professor of Pathology, Harvard Medical School, Boston. Pp. 498; 117 tables; 61 figures. New York: Oxford University Press, 1942. Price, $8.00.

THIS is a comprehensive study of lymph node metastases in neoplastic disease, combining an extensive review of the literature with a large amount of original research. The latter includes an analysis of numerous clinical

cases observed at the Massachusetts General Hospital, the Collis P. Huntington Memorial Hospital, and the Pondville Hospital. No attempt was made to deal with the entire field of neoplasia; but a statistical analysis is presented of 5481 original cases of carcinoma of the skin, breast, mouth, pharynx, larynx, anus, vulva, penis and scrotum, of melanoma of the skin, and of some sarcomata. Other cancers were reviewed but not statistically analyzed, the experiences of the authors being correlated with opinions and experiences recorded in the literature.

In the first part of the book the authors discuss the anatomy of the lymphatic drainage areas of the neck, axilla and arm, groin, pelvis and abdomen, and thorax. In the second and main part they present a detailed analysis of the incidence of lymph node metastases in various cancers; a correlation between the incidence of metastases and such characteristics of the original tumor as the size, duration, grade of malignancy, and other clinical manifestations; and last but not least the results obtained with dissection of lymph nodes and their treatment with radiation. In the third and last part the authors describe the operations on various lymph nodes including miscellaneous operative procedures such as biopsy and radium implantation.

The text is clearly written and the material well organized and concisely presented. The book represents an important contribution to the knowledge of cancer and should be equally valuable to the surgeon, radiologist and pathologist, as it is no longer necessary that decisions in regard to the proper management of the regional lymph nodes in neoplasia be made or modified on the basis of tradition, opinion or prejudice. We now have an excellent book which furnishes abundant information as to the likelihood of metastatic involvement, and as to the curability of involved nodes when they are present.

W. E.

Love Against Hate. By Karl Menninger, M.D., with the collaboration of Jeanette Lyle Menninger. Pp. 311. New York: Harcourt, Brace & Co., 1942. Price, $3.50.

This book presents an interesting discussion of the emotional life written primarily for the layman. The practising physician meets many of the problems which are discussed in it. He will not find much that is essentially new, but will have his own thoughts clarified in the field of the emotional life.

The author rightly points out the failure of patients to consult their physicians on matters of sexual frustration, and, more important still, that physicians generally neglect to investigate them. He correctly states that the teaching of sexuality is still taboo in the medical schools of American universities in spite of the fact that psychiatrists see many dramatic examples in their daily lives which they cannot forget.

The unhappiness which results from sexual frustration plays such an important rôle in life and receives so little attention from physicians, that the reader of this review, if he practises medicine, would do well to not only read but study the volume and others on the same subject.

D. M.

Fundamentals of Immunology. By William C. Boyd, Ph.D., Associate Professor of Biochemistry, Boston University, School of Medicine; Associate Member, Evans Memorial, Massachusetts Memorial Hospitals, Boston, Mass. Pp. 446; 45 illustrations, 67 tables. New York: Interscience Publishers, Inc., 1943. Price, $5.50.

The fundamentals of immunology are presented for the benefit of medical students, chemists, biologists, and others interested in an understanding of the basic principles of the science. The material is aimed at the beginner; but the book will also be useful to the professional immunologist, as the author has used smaller type for material of more interest to the advanced student or professional immunologist. The modern views on a subject are usually

given first, omitting the historical development of a subject in order to conserve space; but the author is not dogmatic and discusses controversial points. The book has a well-organized table of contents, a good index, and a list of references appended to each chapter. The emphasis is on serology. The last chapter, comprising 88 pages (about one-fifth of the book) is devoted to laboratory and clinical techniques employed in the field of immunology. The subject matter is presented very clearly and concisely and printed in a practical style. It is a book which every student of medicine will want to read to bring his knowledge up to date in a field which is being actively worked. H. M.

EMOTIONS AND MEMORY. By DAVID RAPAPORT, PH.D., Head of the Department of Psychology, The Menninger Clinic, Topeka, Kan. Foreword by FRANK FREMONT-SMITH, M.D. Pp. 282. Baltimore: The Williams & Wilkins Company, 1942. Price, $3.00.

IN disorders wherein the emotional element has been potent, repression, distortion or displacement have usually occurred, thus rendering the emotionally charged memories unavailable to the examining physician. In this monograph the writer has scrutinized the literature of psychology, psychopathology and psychoanalysis, to determine the relationship between the emotions and remembering; doing so has led him to suggest a new theory of memory function: "... the memory laws based on logical 'meaning' and 'organization' of the memory material refer only to special cases of memory organization; the more general theory of memory is the theory based on 'emotional organization' of memories—in other words, on the organization of memory strivings."

The chapter on Contributions of Psychoanalysis speaks of the "wholesale forgetting of childhood memories," ... as "an amnesia determined by the inhibition imposed on the evolving infantile sexuality." Direct Experimental Evidence includes a brief but lucid account of the important Rorschach Test. Under Contributions of Hypnosis, the discussion of drugs is too scant, and no mention is made of marijuana which often causes its votaries to recall things long forgotten. The bibliography of this stimulating contribution to mentality is immense. N. Y.

FOOD POISONING. By G. M. DACK, PH.D., M.D., Associate Professor of Bacteriology, University of Chicago. Pp. 138; 13 tables. Chicago: The University of Chicago Press, 1943. Price, $2.00.

A COMPACT compilation of the more recent facts on food poisoning with sections on Chemicals, Poisonous Plants and Animals, Botulism, Staphylococci, the Salmonella, viridans Streptococci, other bacteria related to food poisoning, and Infections to be differentiated from true "Food Poisoning." The author treats each type authoritatively, stressing symptoms, epidemiology, pathology, and laboratory methods in establishing a correct diagnosis in any outbreak of food poisoning. He cites specific cases as well as experimental evidence to illustrate each type. Not written as a textbook, it is ideal as a handbook and reference book for public health, medical and industrial food workers, as well as food technicians, especially those in the armed forces. This book could be used to good advantage by home economics and bacteriology instructors as a reference text. F. E.

OVARIAN TUMORS. By SAMUEL H. GEIST, M.D., Attending Gynecologist, Mount Sinai Hospital; Clinical Professor of Gynecology, College of Physicians and Surgeons, Columbia University, New York. Pp. 527; 312 illustrations. New York and London: Paul B. Hoeber, Inc., 1942. Price, $10.50.

THIS monograph, summarizing our knowledge of ovarian tumors, is appropriate because of the increase in our understanding of embryology, gross and

microscopic anatomy, pathology and physiology of the ovary. The author has based his studies on over 1100 cases of benign and malignant tumors of the ovary. In addition he has incorporated the findings and opinions of many other contributors in this field, supplying thereby an extensive bibliographic list at the end of each chapter. "Not only are the anatomy and physiology of ovarian neoplasms discussed, but an attempt has been made to explain the basis of the symptoms. Association of ovarian neoplasms with other conditions such as pregnancy, and the procedure and care in such cases have been elaborated. Necessarily, new points of view dealing with the origin, classification, and symptomatology of ovarian tumors have been expressed, since progress in this field in the past fifteen years has been so great." The material is well illustrated with both gross and many fine microscopic photographs. This book should be of definite value to all interested in this phase of medicine.

M. T.

A Surgeon's Fight to Rebuild Men—An Autobiography. By Fred H. Albee, M.D., F.A.C.S., F.I.C.S. Foreword by Lowell Thomas. Pp. 349; 11 illustrations. New York: E. P. Dutton & Co., Inc., 1943. Price, $3.50.

In this volume, written primarily for lay readers, a distinguished pioneer in the field of bone graft surgery presents a readable and popular review of his career. In reading the book one gains the impression that the scientifically creative period of the author's life was concentrated in the years before the first World War. It was during this period that he first applied to bone repair the principles of tree-grafting which he had learned from his grandfather on a Maine farm. In illustrated appendices the author shows in interesting fashion the many applications of the principles of the joiner's art to orthopedic surgery. The middle section of the book is devoted to the organization and operation of the U. S. General Hospital No. 3, in which the author played an important part during World War I. Another outlet for the apparently boundless energy of the writer has been the program of rehabilitation of individuals disabled through industrial injuries, particularly in the state of New Jersey. In more recent years, however, the author's interest has become more and more focused on the development of a private sanitarium in Florida, a project which from the standpoint of scientific medicine is in decided contrast to the author's earlier contributions. The faith which the author expresses in "vitaminization and mineralization" as a "cure-all" for a variety of diseases is something of a departure from his early scientific research. Dr. Albee has filled a rôle of an international medical diplomat through his interest in international societies of surgery and orthopedics and has cultivated a wide quaintance, particularly in South and Central America, through extensive travel abroad. In writing this book he has perhaps succeeded in carrying out his principal aim, but has not, in the Reviewer's opinion, made a noteworthy contribution to literature, medical or otherwise.

J. L.

Indigestion. Its Diagnosis and Management. By Martin E. Rehfuss, Professor of Clinical Medicine, and Sutherland M. Prevost, Lecturer in Therapeutics, Jefferson Medical College, Philadelphia. Pp. 556; 35 tables; 63 figures. Philadelphia and London: W. B. Saunders Company, 1943. Price, $7.00.

In this book, a well-known gastroenterologist presents his personal views on the subjects that are regarded as of clinical importance in connection with the syndrome of indigestion. He discusses somewhat informally the various types of digestive disturbance, their causes, the means available for their recognition and the procedures which he employs for their management. Although allegedly written for the guidance of the busy practitioner, some aspects of the subject, especially gastric analysis and therapy, in which the author has special interest, are covered in great and perhaps unnecessary

detail. In addition to a discussion of diet throughout the book, the last 170 pages are devoted entirely to that phase of treatment. The book is discursive but practical, simple in outline but somewhat confused in its detail. Some condensation would render it more helpful to the clinician; but it is easily readable, contains many important clinical observations and presents a subject that deserves special emphasis at this time when the war has focused attention on diseases of the digestive tract. The illustrations are excellent.

T. M.

MODERN TREATMENT OF VENEREAL DISEASES. By F. T. BURKE, D.S.O., M. B., CH.B. (Glas.), Lieut. Col. (late), Royal Army Medical Corps; formerly Director of the London County Council (Whitechapel) Clinic; Consultant Venereologist in the Public Health Department of the London County Council, etc. Pp. 105; 4 figures, many tables. London: John Bale Medical Publications, Ltd., 1942. Price, 12/6d.

THIS book is based on the author's wide experience with venereal disease that he acquired in the British Army and in venereal disease clinics, especially that of Whitechapel, the largest in England. Col. Burke who died over a year ago, represented characteristic British caution in the use of new remedies. Though his work was brilliant in his day and his mind open in a critical way to new ideas, developments in the field of venereal disease have been so rapid that this posthumous publication appears to experts in the field as already out of date in a number of items in the treatment of syphilis and gonorrhea. One questions, then, the desirability of publication at this time, when speed of adequate treatment, if it has been demonstrated to be really adequate, is especially important.

E. K.

THE SIGHT SAVER. By C. J. GERLING. Pp. 202; frontispiece. New York: Harvest House, 1943. Price, $2.00.

THIS book brings to the layman reliable answers to all questions he might have about the normal eye and its most common ailments. The inadvisability of dealing with non-medical eye practitioners is rightfully repeatedly stressed. Self-treatment, proprietary drugs, and quackery are dealt with in such a manner as to leave no doubt as to their status. The material is, with a few minor exceptions, quite accurate. The disadvantage of much repetition in these 200 pages is offset by its encyclopedic arrangement which makes for easy reference.

F. A.

NEW BOOKS

War Injuries of the Chest. Edited by H. MORRISTON DAVIES, M.A., M.D., M.CH., F.R.C.S., and ROBERT COOPE, M.D., B.Sc., F.R.C.P. Pp. 131; 36 figs. Baltimore: The Williams & Wilkins Company, 1942. Price, $2.00.

An Introduction to Biophysics. By OTTO STUHLMAN, JR., PH.D., Professor of Physics, University of North Carolina. Pp. 375; many figs. and tables. New York: John Wiley & Sons, Inc., 1943. Price, $4.00.

Neurosurgery and Thoracic Surgery. Military Surgical Manuals, Vol. VI. Prepared and Edited by the Subcommittees on Neurosurgery and Thoracic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 310; many figs. Philadelphia: W. B. Saunders Company, 1943. Price, $2.50.

Vascular Sclerosis. By ELI MOSCHCOWITZ, A.B., M.D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York; Physician, Mt. Sinai Hospital, New York. Pp. 179; 43 figs. New York: Oxford University Press, 1942. Price, $3.75.

Vascular Spasm. By ALEXANDER JOHN NEDZEL, M.D., M.S., Associate Professor of Pathology. Pp. 151; 161 figs. Urbana: University of Illinois Press, 1943. Price, $2.75 clothbound, $2.25 paperbound.

Principles and Practice of War Surgery. By J. TRUETA, M.D., Formerly Director of Surgery, General Hospital of Catalonia, University of Barcelona; Assistant Surgeon (E.M.S.), Wingfield-Morris Orthopædic Hospital, Oxford; Acting Surgeon-in-Charge, Accident Service, Radcliffe Infirmary, Oxford. Introduction by OWEN H. WANGENSTEEN, M.D., Minneapolis, Minn. Pp. 441; 144 illus. St. Louis: C. V. Mosby Company, 1943. Price, $6.50.

Chemotherapy of Gonococcic Infections. By RUSSELL D. HERROLD, B.S., M.D. Pp. 140; a few tables. St. Louis: C. V. Mosby Company, 1943. Price, $3.00.

Endoscopic Prostatic Surgery. By ROGER W. BARNES, M.S., M.D., F.A.C.S., Professor of Clinical Urology, College of Medical Evangelists; Chief of Urology Service, White Memorial Hospital and Out-Patient Clinic; Senior Attending Surgeon, Los Angeles County Hospital; etc. Pp. 235; 104 illus. St. Louis: C. V. Mosby Company, 1943. Price, $6.00.

Behind the Sulfa Drugs. A Short History of Chemotherapy. By IAGO GLADSTON, M.D. Preface by PERRIN H. LONG, M.D. Pp. 174. New York: D. Appleton-Century Company, Inc., 1943. Price, $2.00.

Proteins, Amino Acids and Peptides as Ions and Dipolar Ions. By EDWIN J. COHN and JOHN T. EDSALL, Harvard Medical School. Including Chapters by JOHN G. KIRKWOOD, Cornell University, HANS MUELLER, Massachusetts Institute of Technology, J. L. ONCLEY, Harvard Medical School, GEORGE SCATCHARD, Massachusetts Institute of Technology. Pp. 686; many tables and figs. New York: Reinhold Publishing Corp., 1943. Price, $13.00.

Introduction to Organic and Biological Chemistry. By L. EARLE ARNOW, PH.D., M.D., Director of Biochemical Research, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Pa.; Formerly Assistant Professor of Physiological Chemistry, University of Minnesota Medical School, and HENRY C. REITZ, PH.D., Assistant Chemist in the Western Regional Research Laboratory, U. S. Department of Agriculture, Albany, Calif; Formerly Assistant Professor of Agricultural Biochemistry, University of Minnesota. Pp. 736; 90 figs., many tables. St. Louis: C. V. Mosby Company, 1943. Price, $4.25.

Flying Men and Medicine. By E. OSMUN BARR, M.D. Pp. 254; 8 figs. (1 colored plate). New York and London: Funk & Wagnalls Company, 1943. Price, $2.50.

Family Treasures. By DAVID D. WHITNEY, PH.D., Professor of Zoölogy, University of Nebraska. Pp. 299; 234 figs. and some tables. Lancaster, Pa.: The Jacques Cattell Press, 1943. Price, $3.50.

Operating Room Technique. By EDYTHE LOUISE ALEXANDER, R.N., Supervisor of the Operating Rooms of The Roosevelt Hospital, New York; Formerly Supervisor of Operating Rooms, Mountainside Hospital, Montclair, N. J.; Supervisor of Private Pavilion Operating Rooms, New York Hospital. Pp. 392; 221 illus. St. Louis: C. V. Mosby Company, 1943. Price, $3.75.

Acute Infections of the Mediastinum. By HAROLD NEUHOF, M.D., D.S., F.A.C.S., Clinical Professor of Surgery, Columbia University, College of Physicians and Surgeons; Surgeon to Mt. Sinai Hospital; and EDWARD E. JEMERIN, M.D., D.S., F.A.C.S., Associate Attending Surgeon, Sydenham Hospital; Adjunct Surgeon, Beth David Hospital; Senior Clinical Assistant in Surgery and Research Assistant, Mt. Sinai Hospital. Pp. 407; 155 figs. Baltimore: The Williams & Wilkins Company, 1943. Price, $6.00.

Psychology You Can Use. By WILLIAM H. ROBERTS. Diagrams by JAMES MACDONALD. Pp. 246. New York: Harcourt, Brace & Co., 1943. Price, $2.00.

The Medical Clinics of North America. Vol. 27, No. 2. *Symposium on Nutrition.* Pp. 327. Philadelphia and London: W. B. Saunders Company, 1943. Price, $16.00 a year.

NEW EDITIONS

Noxious Gases and the Principles of Respiration Influencing Their Action. By YANDELL HENDERSON and HOWARD W. HAGGARD, from the Laboratory of Applied Physiology, Yale University. American Chemical Society Monograph Series. Second ed. Pp. 294; various tables. New York: Reinhold Publishing Corp., 1943. Price, $3.50.

Diseases of the Nose, Throat and Ear. By WILLIAM L. BALLENGER, M.D., F.A.C.S., Late Professor and Head of the Department of Otology, Rhinology and Laryngology, School of Medicine, University of Illinois; and HOWARD C. BALLENGER, M.D., F.A.C.S., Associate Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital. Eighth ed. Pp. 975; 604 engravings, 27 plates (25 in color). Philadelphia: Lea & Febiger, 1943. Price, $12.00.

Clinical Diagnosis. By JAMES C. TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine; and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation), Head of Division on Clinical Laboratories, Mayo Clinic. Tenth ed. Pp. 911; 380 illus. (32 in color). Philadelphia and London: W. B. Saunders Company, 1943. Price, $6.00.

This edition, appearing 4 years since the last, continues to maintain its high standard and position established in previous editions. While retaining the older and yet useful laboratory procedures, this volume has by necessity grown in size and scope by the addition of new methods of practical and diagnostic value to clinical laboratories. M. T.

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